ENAMINES: SYNTHESIS, STRUCTURE, AND REACTIONS

Edited by

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PREFACE

After much of the groundwork for enamine chemistry had been reported by Mannich and Davidsen in 1936, this area of organic chemistry remained relatively dormant for almost twenty years. Interest in enamines was aroused anew with a publication by Stork and his coworkers in 1954 demonstrating the general utility of enamines for the acylation and alkylation of carbonyl compounds. This interest in enamines continued to grow in the ensuing years as indicated by the increasing number of publications in this area. The scope of enamine chemistry also broadened considerably.

There have been earlier reviews of enamine chemistry, but the field has continued to expand rapidly. The need for a new appraisal of the present state of enamine chemistry thus seemed apparent.

The objective of this book is to review and correlate in depth the synthetic, mechanistic, and physical properties of enamines. This has been done by surveying the field from eight different perspectives. Since these perspectives have certain common areas between them, and since it seemed desirable to allow each contributor to tell his story in its fullest scope and in his own style, there is some overlapping of material between the chapters. However, it is hoped that the difference of viewpoints and context in which this material appears in these chapters will provide the reader with fresh insights and stimulate further research.

The editor wishes to extend his thanks to each of the contributors of this book who so willingly gave of their time and talents, and he wishes to extend his personal gratitude to Dr. Nelson J. Leonard for initially stimulating his interest in enamines and for his continuing interest over the years.

A. GILBERT COOK

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STRUCTURE AND PHYSICAL PROPERTIES OF ENAMINES

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I. Introduction

The term "enamine" was first introduced by Wittig and Blumenthal (*1*) as the nitrogen analogue of the term "enol."

Since the electron pair on the nitrogen atom can overlap with the π electrons of the double bond, the enamines are capable of existing in two

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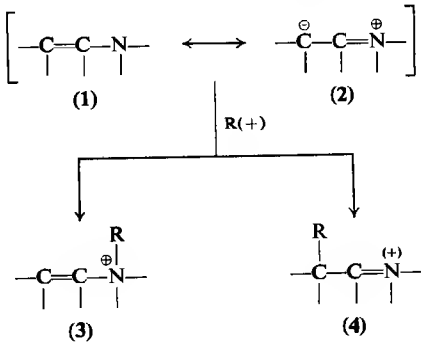
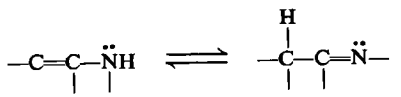
mesomeric forms (**1** and **2**). The electrophilic attack may occur either at the nitrogen atom of the enamine to give an enammonium cation (**3**) or at the β-carbon atom of the enamine to give an iminium cation (**4**).



(1) (2) (3) (4)

This type of mesomerism is much more important in enamines possessing a tertiary nitrogen atom than in those possessing a secondary nitrogen atom since the latter exist largely in the tautomeric imino form (*2*).



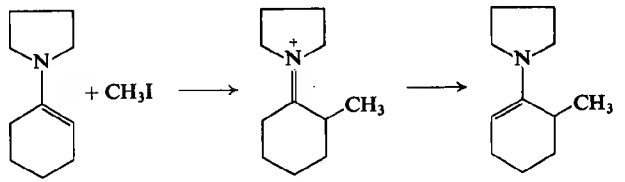
This chapter is devoted mostly to the discussion of the structure and physical properties of the enamines with a tertiary nitrogen atom, the emphasis being on enamines of cyclic ketones.

II. Structure of Enamines

A. Enamines of 2-Substituted Cyclic Ketones

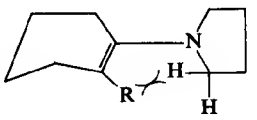
In 1954 Stork et al. (*3*) reported that the alkylation of the pyrrolidine enamine of cyclohexanone (**5**) with methyl iodide followed by acid hydrolysis led to the monoalkylated ketone. It was thus obvious that the enamine (**7**) derived by the loss of proton from the intermediate methylated iminium cation (**6**) failed to undergo any further alkylation.

The pyrrolidine enamine of 2-methylcyclohexanone (**7**) was in fact found to be quite inert toward further alkylation and was shown to consist only of the trisubstituted isomer (*4*) on the basis of the NMR spectral data. The



(5) (6) (7)

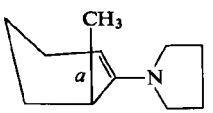
formation of the tetrasubstituted isomer (**8**) was excluded on steric grounds (*4*), since it would involve a severe steric interaction between the methyl group and the methylene group adjacent to the nitrogen atom if an overlap between the electron pair on the nitrogen atom and the double bond were to be maintained. Kuehne (*5*) has reported that the pyrrolidine enamine of



(8)

2-phenylcyclohexanone failed to show any styrene-type absorption in the ultraviolet, which would have been exhibited by the tetrasubstituted isomer.

A rationale for the inert behavior of the enamine **7** toward further alkylation was put forward by Williamson (*6*), who argued that the methyl group in **7** should assume an axial orientation as shown in conformation **9** if the overlap between the electron pair on the nitrogen atom and the double bond is to be maintained, since in the alternate conformation (**10**) the equatorial methyl group is pretty much coplanar with the methylene group adjacent to the nitrogen atom and thus interferes severely with it. The alkylation, being subject to stereoelectronic control would, therefore, involve a severe 1,3-diaxial alkyl-alkyl interaction, thus increasing the energy of the transition state.



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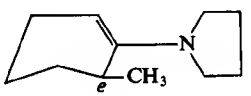
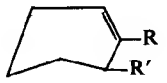


(10)

This type of allylic interaction between the equatorial methyl group and the methylene group adjacent to the nitrogen atom has been recently generalized by Johnson and Malhotra (*7,7a*) as the $A^{(1,2)}$ strain between substituents R and R′ in the cyclohexenyl-type system shown, as in **(11)**, the dihedral angle between the substituents being ~40°. The magnitude of



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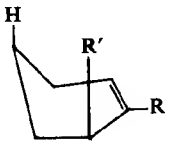
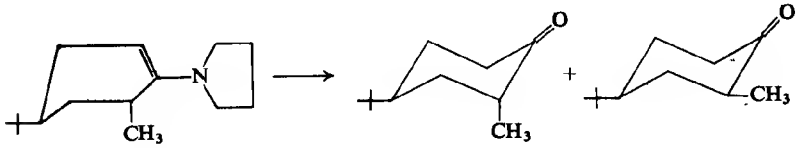


(12)

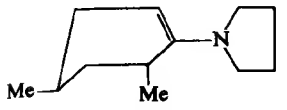
this interaction is dependent upon the size of the substituents. It was suggested by these authors that relief from this strain is readily obtained by conformational inversion to give the conformer **(12)**, in which the dihedral angle between the substituents is increased to 85°. If the magnitude of 1,3-diaxial interaction between the C-2 alkyl group and the C-4 axial hydrogen atom is smaller than that of the $A^{(1,2)}$ strain between the substituents, then the conformer **(12)** would become the favored one.

That the methyl group in the pyrrolidine enamine of 2-methylcyclohexanone (7) is in fact axial was demonstrated by Johnson and Whitehead (*8*). They found that careful hydrolysis of the pyrrolidine enamine of the conformationally more stable system, i.e., 2-methyl-4-*t*-butylcyclohexanone **(13)**, led to a 1:4 mixture of *cis* and *trans* isomers of the ketone **(14** and **15)**, showing that the methyl group in the enamine is largely in the axial orientation.



(13) **(15)** **(14)**

Johnson and Whitehead have further shown that the reductive elimination of the pyrrolidino group from the pyrrolidine enamine of 2,4-dimethylcyclohexanone **(16)**, which involved treating it with a mixture of lithium aluminum hydride and aluminum chloride (*9*), gave the *trans* isomer of 3,5-dimethyl-Δ^2-cyclohexene **(17)** which on subsequent hydrogenation on a platinum catalyst led to the *trans*-3,5-dimethylcyclohexane **(18)**.



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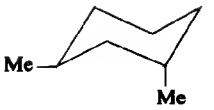
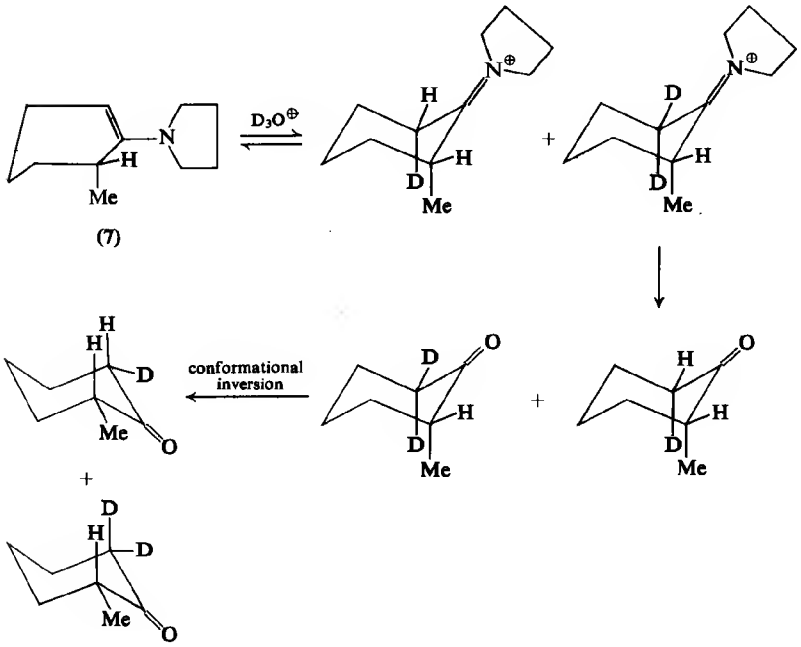


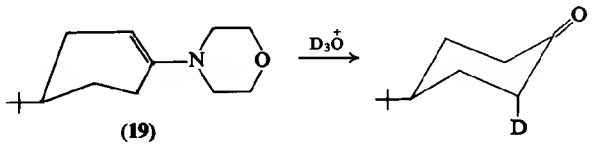
(18)

Malhotra and Johnson (*10*) provided a direct proof for the orientation of methyl group in the enamine (7) by carrying out its hydrolysis at room temperature with 50% deuterioacetic acid–deuterium oxide in diglyme solution. The hydrolysis was found to be over within 5–10 min. The infrared spectrum of the product exhibited in the C—D stretching region a strong band at 2190 cm^{-1} (equatorial C—D) and a medium band at 2220 cm^{-1} ($-CD_2-$), showing it to be a mixture of 6*e*-deuterated (major) and 6,6-dideuterated (minor) ketones. Appearance of the methyl group in the NMR spectrum as a doublet precluded the presence of any deuterium at the 2 position. The *d* incorporation pattern in the ketone was rationalized as shown in Scheme 1. The formation of 6*e*-deuterated species is obviously



Scheme 1

due to the conformational inversion of 6*a*-deuterio-2*a*-methylcyclohexanone, formed by the stereoelectronically controlled protonation of the enamine, to give the thermodynamically more stable conformer 6*e*-deuterio-2*e*-methylcyclohexanone. That the dilute acetic-acid-catalyzed hydrolysis of the enamine was subject to stereoelectronic control was shown by the hydrolysis of the pyrrolidine enamine of 2-methyl-4-*t*-butylcyclohexanone (**13**), which led to a mixture of 6*a*-deuterated (2140 cm^{-1}, C—D axial) and 6,6-dideuterated (2220 cm^{-1}) derivatives of mainly the *trans*-2-methyl-4-*t*-butylcyclohexanone (**15**). Schaefer and Weinberg (*11*) have also demonstrated that the acid-catalyzed deuterolysis of the morpholine enamine of 4-*t*-butylcyclohexanone (**19**) led to the monodeuterated ketone in which the deuterium is axial.



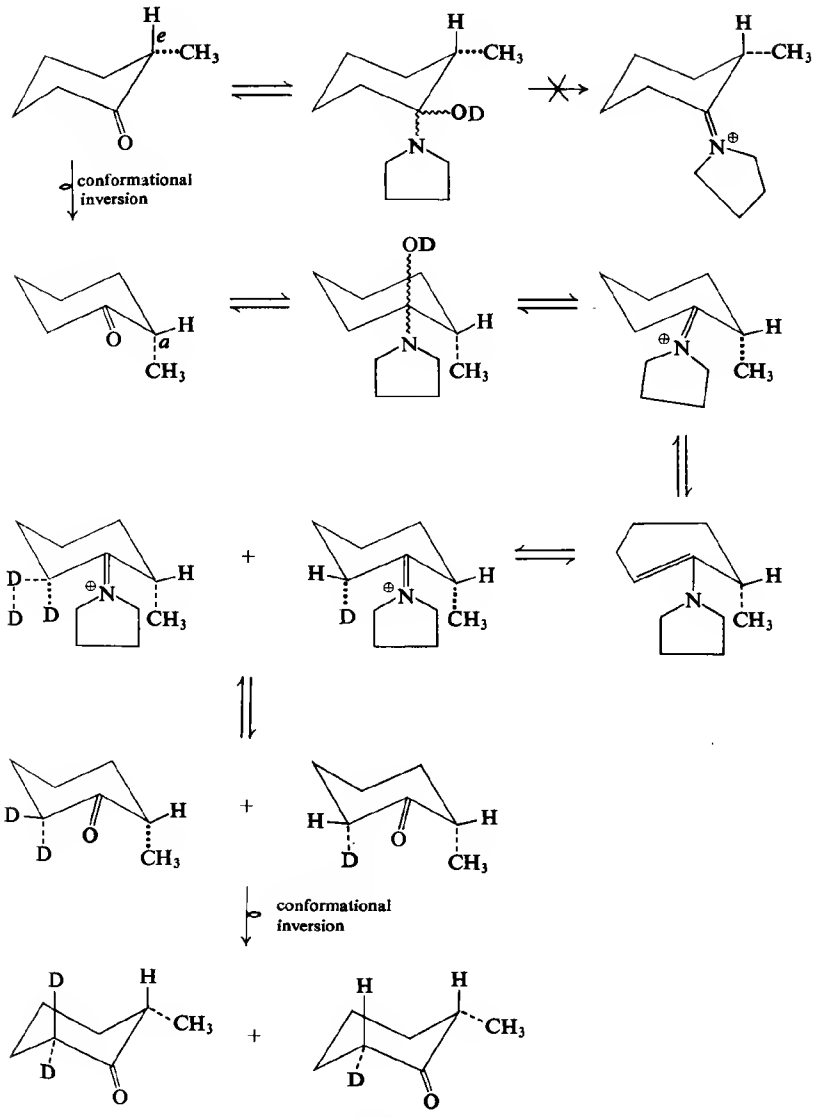
(**19**)

Karady et al. (*12*) report that the alkylation of the pyrrolidine enamine of 4-alkycyclohexanone was found to be subject to stereoelectronic control; the product of hydrolysis under nonequilibrating conditions led largely to the *trans*-2,4-dialkylcyclohexanone.

Malhotra and Johnson (*10*) have further shown that 2-methylcyclohexanone on treatment with 1 equivalent of pyrrolidine and 1.5 equivalents of 50% deuterioacetic acid–deuterium oxide in diglyme solution for 1 hr gave a mixture of 6*e*-deuterated and 6,6′-dideuterated ketones. The formation of these deuterated species was explained by the mechanistic sequence outlined in Scheme 2.

Since the conformational inversion of 2*e*-methylcyclohexanone is the key step in this sequence, the corresponding conformationally more stable system, i.e., *cis*-2-methyl-4-*t*-butylcyclohexanone (**14**), should fail to incorporate any deuterium. This was actually shown to be the case. Treatment of this ketone under identical conditions for *d* exchange did not show any *d* incorporation. This evidence also rules out the likelihood of any *d* incorporation via acid- or base-catalyzed enolization.

Unlike the pyrrolidine enamine of 2-methylcyclohexanone (**7**), which consists predominantly of the trisubstituted isomer, the morpholine and piperidine enamines of 2-methylcyclohexanone (**20** and **21**) were shown by



Scheme 2

Gurowitz and Joseph (*13*) as an almost 1:1 mixture of tri- and tetrasubstituted isomers by NMR spectroscopy. The results for various enamines are described in Table 1.

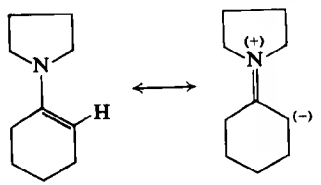
TABLE 1

Isomer Distribution of Enamines of 2-Methylcyclohexanone

Amine	Per cent trisubstituted isomer	Per cent tetrasubstituted isomer	Ref.
Pyrrolidine	90	10	*13*
Morpholine	52	48	*13*
Piperidine	46	52	*13*
Diethylamine	25	75	*13*
N-Methylaniline	0	100	*15*

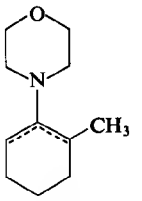
The increase in the proportion of the tetrasubstituted isomer in the cases of the morpholine and piperidine enamines of 2-methylcyclohexanone has been ascribed to both steric and electronic factors. The authors propose that the overlap of the electron pair on the nitrogen atom and the π electrons of the double bond is much more important in the case of the pyrrolidine enamines and much less with the others. Support for this postulate was provided by the NMR spectra of these enamines, wherein the chemical shifts of the vinylic protons of the pyrrolidine enamines were at a higher field than those of the corresponding morpholine and piperidine enamines by 20–27 Hz. The greater amount of overlap or electron delocalization, in the case of pyrrolidine enamine, is in accord with the postulate of Brown et al. (*14*) that the double bond exo to the five-membered ring is more favored than the double bond exo to the six-membered ring.

Since the overlap requirements with the piperidine and morpholine enamine are much less stringent, the steric interference in the tetrasubstituted

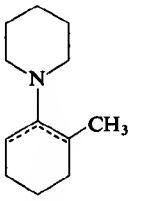


isomer is therefore diminished. Consequently, this isomer becomes of equal or greater stability than the trisubstituted isomer.

Another case in point is the N-methylaniline enamine of 2-methylcyclohexanone (**22**), which has been reported (*15*) to consist exclusively of the tetrasubstituted isomer. Here the electron pair on the nitrogen atom could



(**20**)



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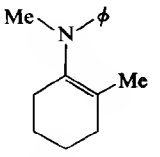
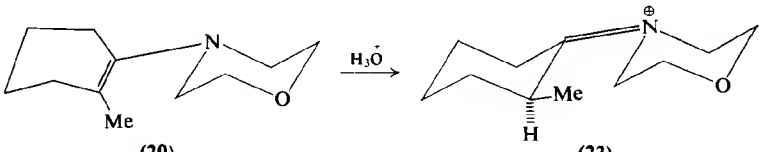


(**22**)

overlap predominantly with the phenyl group and not with the enamine double bond, thus minimizing the steric interference between the C-2 methyl group and the substituents attached to nitrogen.

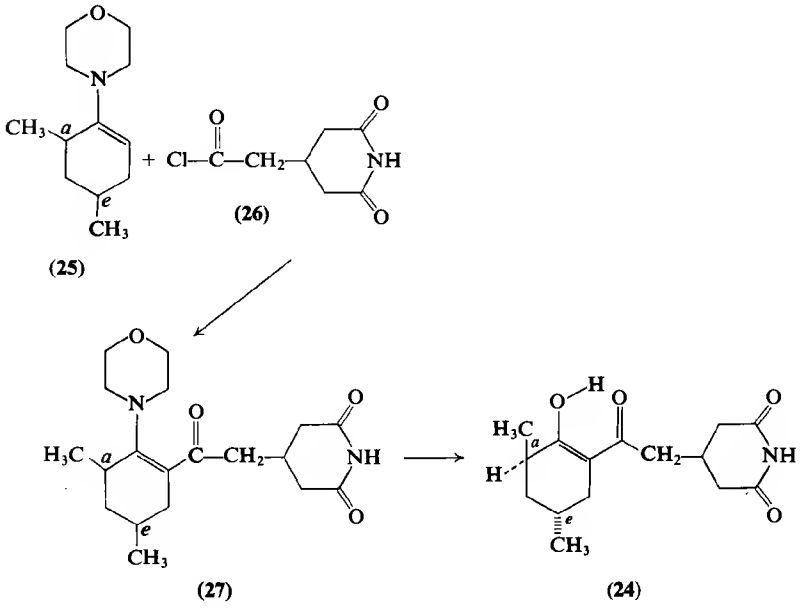
Morpholine enamine of 2-*n*-propylcyclohexanone has been shown (*16*) by NMR spectroscopy to be a 2:3 mixture of tri- and tetrasubstituted isomers.

The tetrasubstituted isomer of the morpholine enamine of 2-methylcyclohexanone (**20**) because of the diminished electronic overlap should be expected to exhibit lower degree of enamine-type reactivity toward electrophilic agents than the trisubstituted isomer. This was demonstrated to be the case when the treatment of the enamine with dilute acetic acid at room temperature resulted in the completely selective hydrolysis of the trisubstituted isomer within 5 min. The tetrasubstituted isomer was rather slow to react and was 96% hydrolyzed after 22 hr (*17*). The slowness might also be due to the intermediacy of quaternary iminium ion **23**, which suffers from a severe $A^{(1,3)}$ strain (*7,7a*) between the equatorial C-2 methyl group and the methylene group adjacent to the nitrogen atom, **23** being formed by the stereoelectronically controlled axial protonation of **20**.



(**20**) (**23**)

That the methyl group in the less substituted isomer of the enamine (**20**) is axial was borne out by the work of Johnson et al. (*18*) in the total synthesis of the glutarimide antibiotic *dl*-dehydrocycloheximide (**24**). The acylation of the morpholine enamine of 2,4-dimethylcyclohexanone (**25**) with 3-glutarimidylacetylchloride (**26**), followed by the hydrolysis of the intermediate product (**27**) with an acid buffer, led to the desired product in 35% yield. The formation of the product in a rather low yield could most probably be ascribed to the relatively low enamine-type activity exhibited by the tetrasubstituted isomer, which fails to undergo the acylation reaction, and also because in trisubstituted isomer one of the CH_3 groups is axial. Since the methyl groups in the product are *trans* to each other, the allylic methyl group in the less substituted isomer of the enamine should then be in the axial orientation.

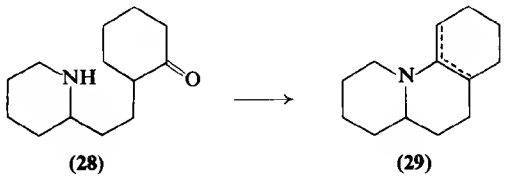


(25) (26) (27) (24)

Schaeffer and Jain (*19*) have also reported the synthesis of optically active dehydrocycloheximide (*24*) by using optically active piperidine enamine derived from (+)-*trans*-2,4-dimethylcyclohexanone.

The presence of 1,3-diaxial interaction between the C-2 alkyl group and the C-4 axial hydrogen atom is reflected in the rate of enamine formation of 2-substituted cyclohexanone. It has been shown by Hunig and Salzwedel (*20*) that even under forcing conditions, the yield of pyrrolidine and morpholine enamines of 2-methylcyclohexanone does not exceed 58%, whereas the C-2 unsubstituted ketones underwent enamine formation under rather milder conditions in better than 80% yield.

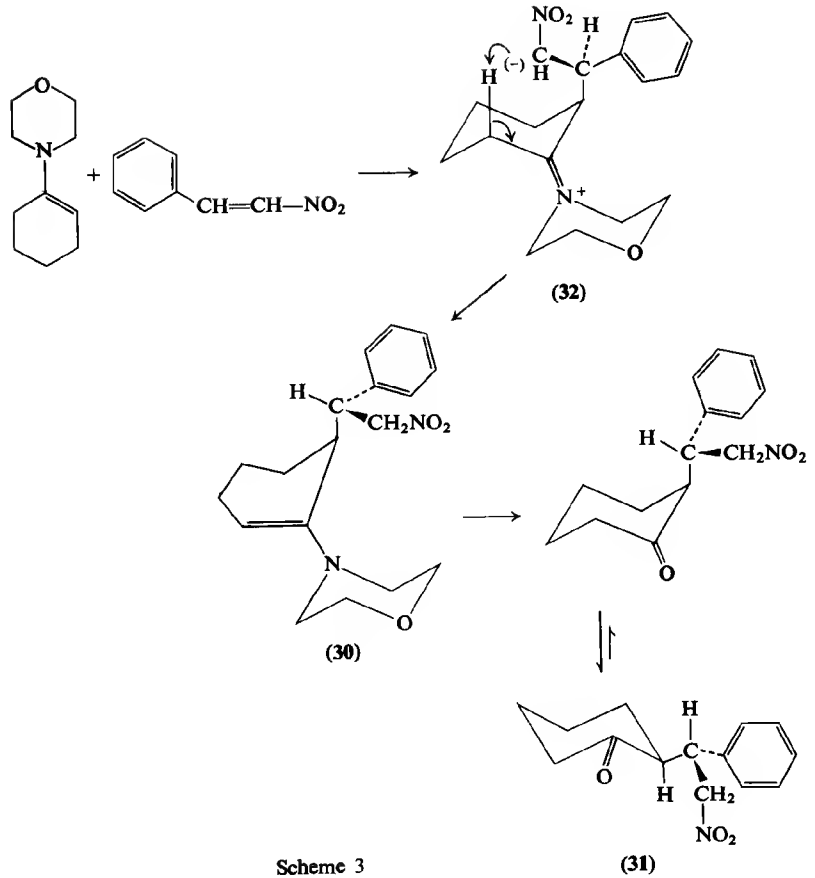
Danishafsky and Feldman (*21*) have shown that the cyclization of the aminoketone (**28**) led to the internal enamine (**29**), which lacks the steric interaction of the type existent in the enamines of 2-alkycyclohexanones. In this case, the tetrasubstituted isomer was favored over the trisubstituted one by a factor of 4:1, which may be ascribed to the double bond being in the exo position in the latter case.



(28) (29)

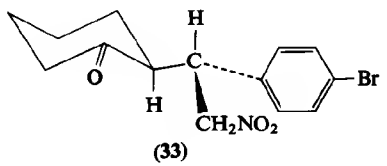
Risaliti et al. (*22*), have shown that in the addition of the electrophilic olefins to the enamines of cyclohexanone, the formation of the less substituted enamine is favored when a bulky group is present at the electrophilic carbon atom. For instance, the reaction of β-nitrostyrene with the morpholine enamine of cyclohexanone gave only the trisubstituted isomer (**30**) with the substituent in the axial orientation (*23*). The product on hydrolysis led to the ketone (**31**) to which erythro configuration was assigned on the grounds illustrated in Scheme 3 (*24*).

In the more stable conformation the substituent in the dipolar intermediate (**32**) is axial since the equatorial substituent in the alternate conformation interferes sterically with the methylene group adjacent to the nitrogen atom. Furthermore, the phenyl group, in order to avoid interference with the cyclohexane ring, assumes the anti conformation with respect to the ring, while the β-carbon atom bearing the negative charge is suitably disposed for the intramolecular transference of the axial hydrogen atom from the C-6 carbon atom to give the enamine (**30**). Hydrolysis of (**30**) furnishes the



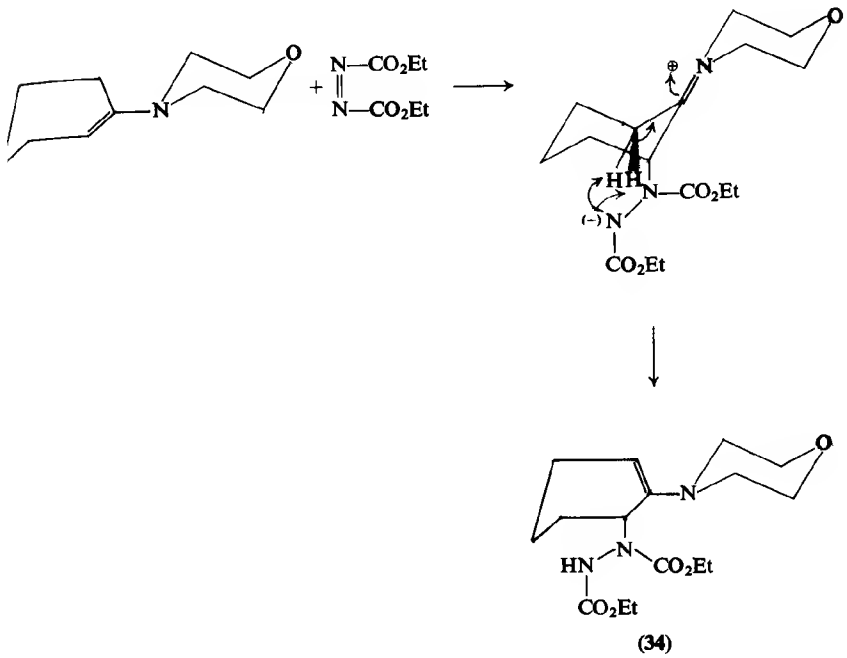
Scheme 3

ketone (**31**) possessing the erythro configuration. Support for this assignment was provided by X-ray analysis of the ketone (**33**) with the substituent bearing a *p*-bromophenyl group.



(**33**)

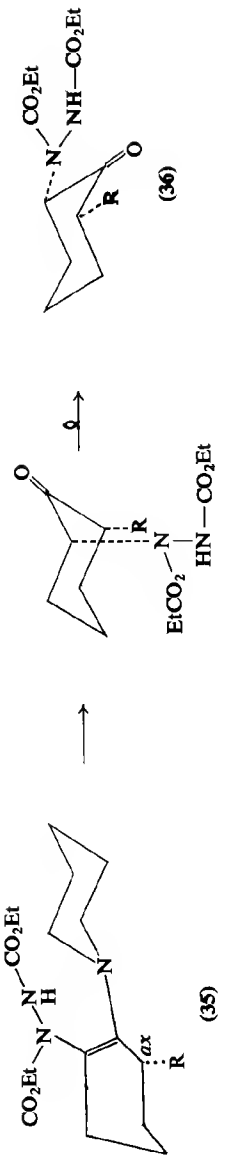
In a similar manner the addition of ethyl azodicarboxylate to the morpholine enamine of cyclohexanone furnished the less substituted isomer (**34**) with the substituent in the axial orientation (*25,26*).



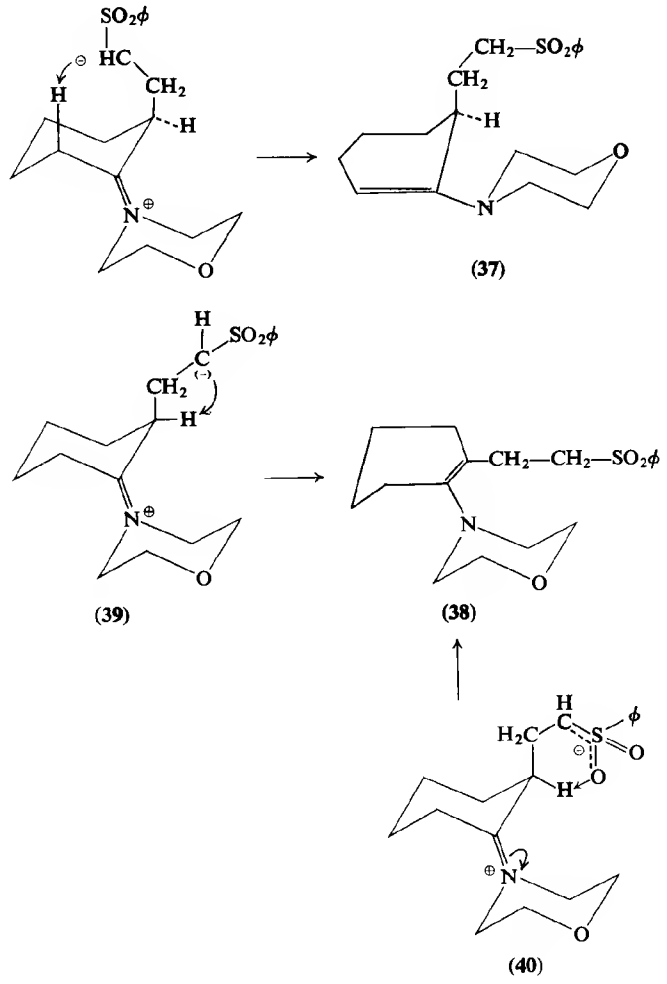
(**34**)

It would be pertinent to point out (*25,27*) that the trisubstituted isomer of the enamine of 2-alkylcyclohexanone reacts in a quantitative manner with ethyl azodicarboxylate to give the addition product (**35**). This reaction in conjunction with NMR spectroscopy can thus be employed for the determination of the amount of the trisubstituted isomer. According to the authors, hydrolysis of **35** furnishes the corresponding *cis*-2,6-disubstituted cyclohexanone (**36**); this seems unlikely since it would involve the stereoelectronically unfavored equatorial protonation of the enamine.

However, when the bulky substituent is no longer present at the electrophilic carbon atom, the addition of the olefin to the morpholine enamine of cyclohexanone leads largely to the tetrasubstituted isomer. For instance the reaction of this enamine with phenyl vinyl sulfone gave a 1 : 3 mixture of



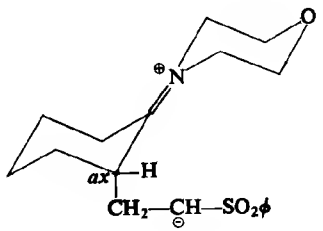
the tri- and tetrasubstituted isomers (**37** and **38**) of the enamine (*23*). The suggested pathway is (*26*) outlined in Scheme 4 for the formation of these isomers.



Scheme 4

The formation of the less favored trisubstituted isomer (**37**) occurs by the usual intramolecular axial proton transfer from the 6 position, whereas that of the tetrasubstituted isomer (**38**) involves the intramolecular proton transfer of the stereoelectronically less favored equatorial proton either via a four-membered transition state (**39**) or a six-membered transition state (**40**).

The preferred formation of the tetrasubstituted isomer with the olefin without any bulky substituent at the electrophilic carbon atom is undoubtedly due to the preponderance of that conformation of the dipolar intermediate in which the substituent is syn to the morpholine group, as shown in (**41**). The situation is, however, reversed in case of the olefin with



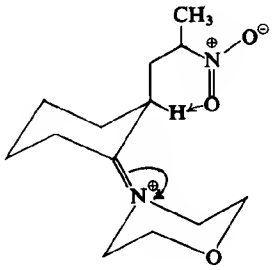
(**41**)

a bulky substitutent at the electrophilic carbon, where the anti conformation becomes the predominant one.

Reaction of the pyrrolidine enamine of cyclohexanone with phenyl vinyl sulfone afforded a 9:1 mixture of the tri- and tetrasubstituted isomers (*26*). The preference of the less substituted isomer in this case is in keeping with the greater overlap requirement between the π electrons of the double bond and the electron pair on the nitrogen atom, since the double bond exo to the five-membered ring is much more favored than the double bond exo to the six-membered ring. It is, however, hard to explain the formation of largely the trisubstituted isomer with the piperidine enamine of cyclohexanone, where both of the rings involved are six-membered.

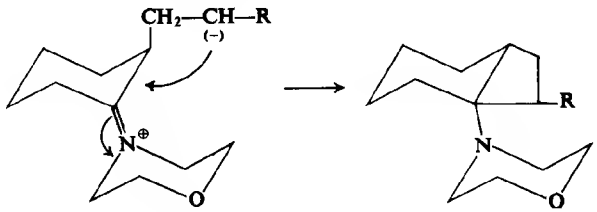
Risaliti et al. (*23*) have also studied the addition of 2-nitropropene, which also lacks any substituent at the electrophilic carbon atom, to the morpholine enamine of cyclohexanone. The product, as expected, was the tetrasubstituted isomer, the formation of which may be envisioned via the transition state (**42**).

It is appropriate to point out that when the enamine was allowed to react with the olefin in nonpolar solvents such as benzene, cyclohexane, or ethyl



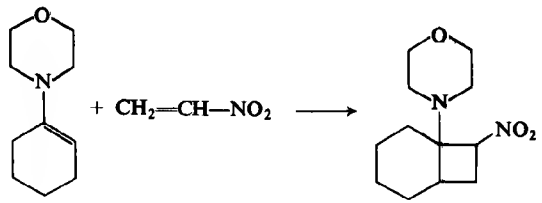
(**42**)

ether, the intermediate zwitterion (**43**) did not collapse to give the cycloaddition product, of the type (**44**) (*28*). This may be attributed to the steric compression provided by the bulky substitutent present at the α- or β-carbon

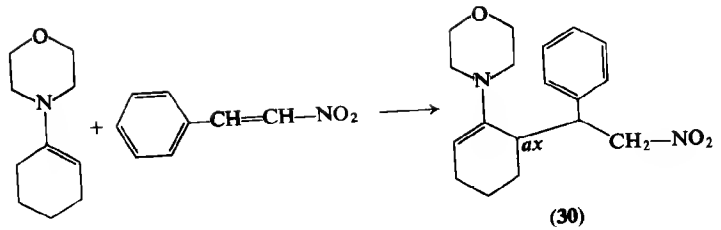


(**43**) (**44**)

atom of the olefin. For instance, Kuehne and Foley (*29*) have found that whereas the reaction of morpholine enamine of cyclohexanone or of cyclopentanone with nitroethylene at 0° in petroleum ether led to the aminocyclobutane product (**45**), the reaction of the enamine with β-nitrostyrene under identical conditions led to the less substituted isomer of alkylated enamine (**30**), thus corroborating the results of Risaliti et al. (*23*).



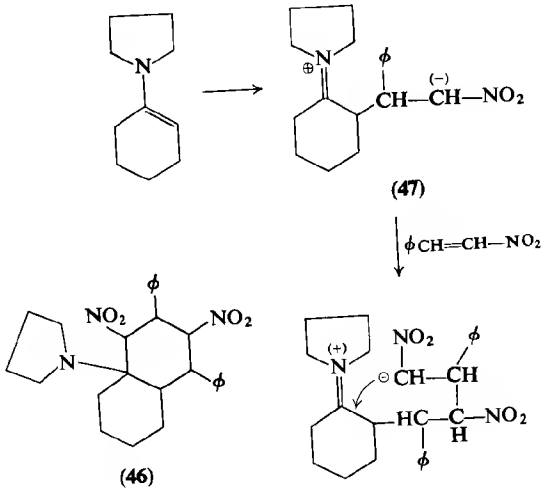
(**45**)



(30)

Although the enamine (**30**) underwent addition reaction with ethyl azidodicarboxylate, it failed to add another mole of β-nitrostyrene. In a similar manner the morpholine enamine of 2-methylcyclohexanone also failed to react with this olefin, i.e., β-nitrostyrene, which is undoubtedly due to the 1,3-diaxial interaction between the methyl group and the incoming electrophile in the transition state.

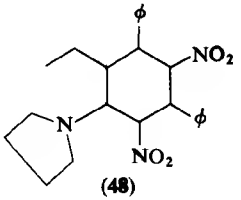
It was, however, found (*22*) that when the pyrrolidine enamine of cyclohexanone was allowed to react with an excess of β-nitrostyrene, a bis adduct (**46**), made up of one molecule of the enamine and two molecules of olefin, was obtained in addition to the monoadduct. That the bis adduct is not derived from the monoadduct was shown by the latter's failure to react with β-nitrostyrene. Therefore, this adduct must be formed by the addition of the olefin to the dipolar intermediate (**47**), as shown in the following scheme.



(47)

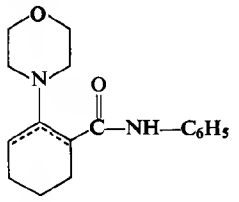
(46)

Kuehne and Foley (*29*) have found that the reaction of the pyrrolidine enamine of butyraldehyde with 2 equivalents of β-nitrostyrene also led to a bis adduct with the structure as shown in **48**.

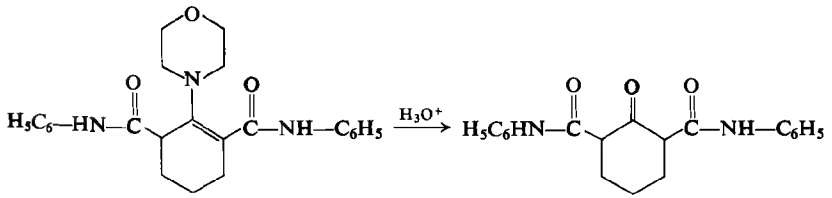


(48)

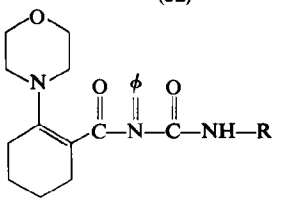
The reaction of morpholine enamine of cyclohexanone with 1 mole of phenyl isocyanate has been reported (*30,31*) to give the monoadduct (**49**), consisting largely of the trisubstituted isomer, and with 2 moles of phenyl isocyanate, the bis adduct (**50**). That the bis adduct is a dicarboxyanilide rather than a urea derivative (*32*) such as **51** was shown by its mild hydrolysis to the ketone (**52**). Reaction of the morpholine enamine of 2-methylcyclo-



(49)

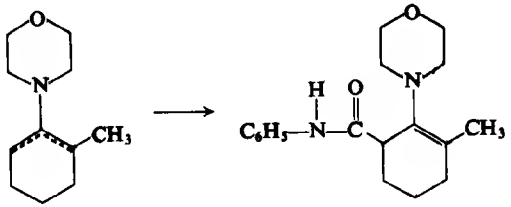


(50) (52)



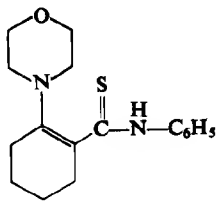
(51)

hexanone (**20**), which has been shown to be a 1:1 mixture of tri- and tetra-substituted isomers (*13*), with 1 mole of phenyl isocyanate led to the enamine (**53**) in 82% yield, indicating that isomerization of the tetrasubstituted isomer of the starting material to the trisubstituted isomer occurs during the reaction.



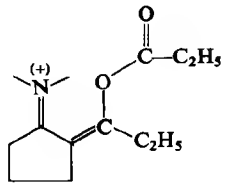
(**20**) (**53**)

The reaction of the morpholine enamine of cyclohexanone with phenyl isothiocyanate led only to the tetrasubstituted isomer of the monoadduct (**54**), which failed to add any more of the phenyl isothiocyanate. The formation of only the tetrasubstituted isomer has been attributed by Hunig et al. (*31*) to the stronger conjugation of the C=S group with the enamine double bond than that of the C=O group in the enamine (**49**).

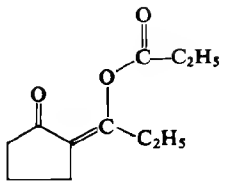


(**54**)

In their original communication on the alkylation and acylation of enamines, Stork et al. (*3*) had reported that the pyrrolidine enamine of cyclohexanone underwent monoacylation with acid chlorides. For example, the acylation with benzoyl chloride led to monobenzoylcyclohexanone. However, Hunig and Lendle (*33*) found that treatment of the morpholine enamine of cyclopentanone with 2 moles of propionyl chloride followed by acid hydrolysis gave the enol ester (**56**), which was proposed to have arisen from the intermediate (**55**).

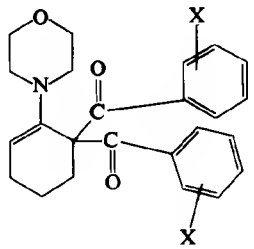


(**55**)



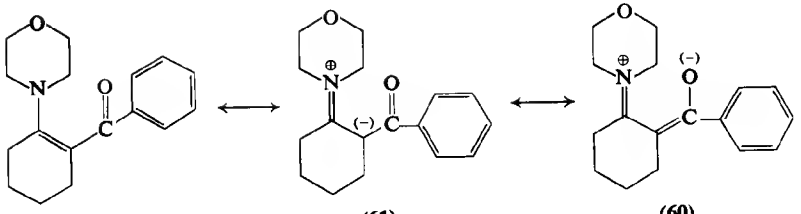
(**56**)

Campbell and Jung (*34*) have reported that the reaction of 2 moles of *o*-halo-substituted benzoyl chloride with the morpholine enamine of cyclohexanone gave the corresponding 2,2-dibenzoyl derivative (**57**).

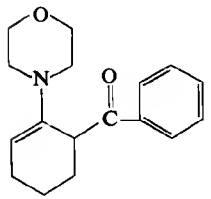


(**57**)

The presence of the conjugation between the enamine double bond and the benzoyl group was proposed as the controlling factor in the initial formation of the tetrasubstituted isomer (**58**) as opposed to the trisubstituted isomer (**59**), which lacks this conjugation. The preference of the C acylation over O acylation was ascribed to the steric strain between the carbonyl oxygen and the methylene group adjacent to the nitrogen atom in the resonance form (**60**), thus suppressing the negative character of the oxygen atom and decreasing the probability of O acylation. Therefore C acylation takes place because of the large contribution of the resonance form (**1**). The lowest energy conformation of resonance from **61** would have the benzoyl group axial, since in the alternate orientation there would be $A^{(1,3)}$ strain between this grouping and the methylene group adjacent to the nitrogen atom. The second benzoyl group would then come in from the stereoelectronically less favored equatorial direction. Helmers (*35*), however, has



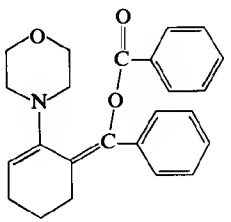
(58) (61) (60)



(59)

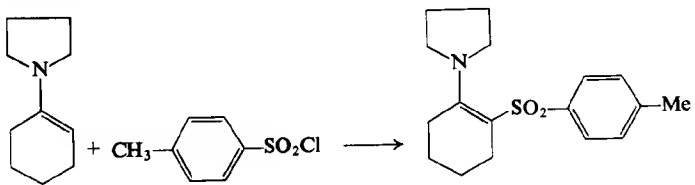
(57)

recently reported that further benzoylation of the morpholine enamine of 2-benzoylcyclohexanone (**58**) led to the enol ester (**62**) whose structural assignment was based on NMR, UV, and IR spectral data.



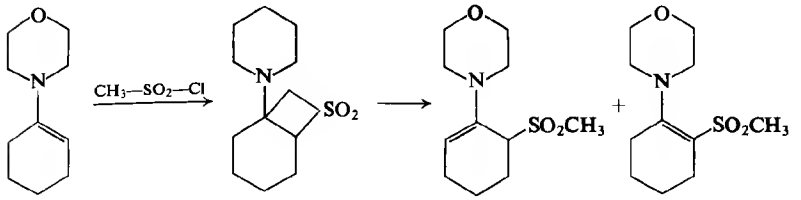
(62)

Stork and Borowitz (*36*) have reported that the reaction of the pyrrolidine enamine of cyclohexanone with aromatic sulfonyl chloride led to the tetrasubstituted isomer of the sulfonated enamine (**63**).



(63)

The reaction with methanesulfonyl chloride in the presence of a proton abstracter like triethyl amine gave not the enamine, but a cyclic aminosulfone (**64**).

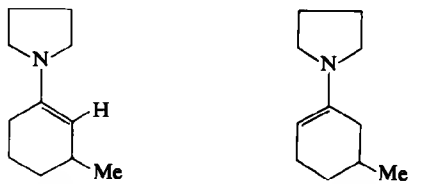


(64) (65) (66)

The reaction has been suggested (*37*) to proceed via the addition of sulfene $CH_2{=}SO_2$. The aminosulfone (**64**), on heating, gave a 2:1 mixture of tri- and tetrasubstituted isomers (**65** and **66**).

B. Enamines of 3-Substituted Cyclic Ketones

Malhotra et al. (*38*) found that the pyrrolidine enamine of 3-methylcyclohexanone, prepared under equilibrating conditions, is a 3:7 mixture of Δ' and Δ^6 isomers (**67** and **68**) on the basis of NMR spectral data. The preponderance of the Δ^6 isomer in the mixture was attributed to $A^{(1,2)}$ strain between the equatorial methyl group and the vinylic hydrogen atom

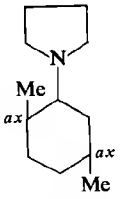


(67) (68)

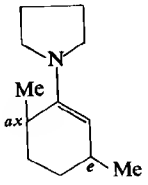
in the Δ' isomer. The magnitude of this allylic strain has been estimated to be 0.6–0.7 kcal/mole. Studies by Williams et al. (*16*) were in accord with these results. They found that the morpholine enamine of 3-methylcyclohexanone consisted of a 1:2 mixture of Δ' and Δ^6 isomers.

Further proof regarding the magnitude of $A^{(1,2)}$ strain between the methyl group and hydrogen comes from the isomeric composition of the enamine

derived from 2,5-dimethylcyclohexanone. It was found to be a 2:3 mixture of the isomers (**69**) and (**70**) by NMR spectroscopy, thus giving a value of ca. 0.30 kcal/mole for the free energy difference between the two isomers (*38*).



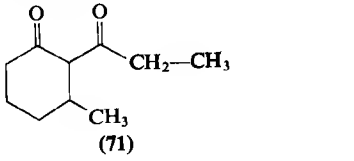
(**69**)



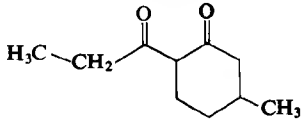
(**70**)

This value is in excellent agreement with the calculated free energy value by the consideration of various nonbonded interactions in the epimers (**69** and **70**) [(2 × 1,3-diaxial Me—H interaction) − (1 × 1,3-diaxial Me—H interaction + 1 × 1,2-$A^{(1,2)}$ Me—H interaction) = (0.9 × 2) − (0.9 + 0.6) = 0.3 kcal/mole]. Hydrolysis of the enamine with dilute acetic acid gave a 3:2 mixture of *cis* and *trans* isomers of the ketone, thus confirming the assignments made to the enamine components.

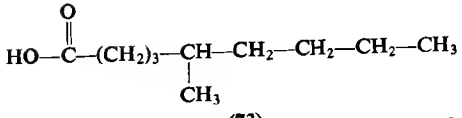
Hunig and Salzwedel (*20*) report that the acylation of the pyrrolidine enamine of 3-methylcyclohexanone with propionylchloride followed by the hydrolysis and the base cleavage of the resulting dione isomers (**71**) and (**72**) and subsequent reduction of the keto groups gave a 3:7 mixture of the carboxylic acids (**73** and **74**), respectively. Vig et al. (*39*), however, found



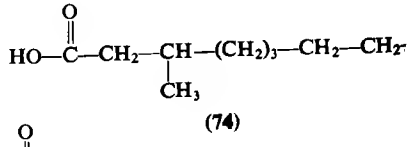
(**71**)



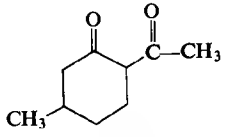
(**72**)



(**73**)



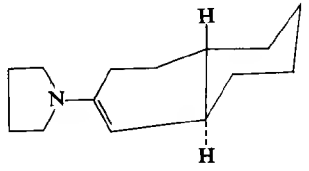
(**74**)



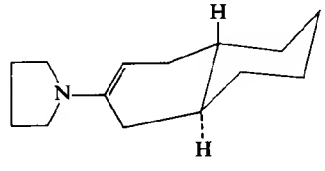
(**75**)

that the acetylation of this enamine led mainly to 2-acetyl-5-methylcyclohexane (**75**), showing that acetylation of the Δ' isomer (**67**) is subject to steric hindrance between the C-3 methyl group and the incoming acetyl group at the C-2 position.

Trans-2-decalone, the skeletal arrangement of which is similar to that of 3-methylcyclohexanone, in which the methyl group is largely in the thermodynamically preferred equatorial orientation, when allowed to react with pyrrolidine formed a 28:72 mixture of Δ' and Δ^2 isomers (**76** and **77**). The isomer ratio was based on NMR spectral data. The preference of the Δ^2 isomer in this case can be attributed to the $A^{(1,2)}$ strain between the C-8 methylene group and the C-1 vinylic proton in the Δ' isomer (*38*).

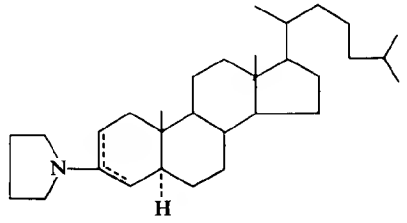


(**76**)



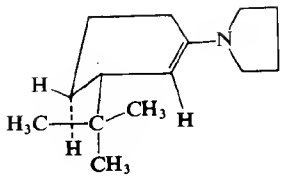
(**77**)

In the steroidal series Heyl and Herr (*40*) have reported that the pyrrolidine enamine of 5α-cholestan-3-one consisted of a mixture of Δ^2 and Δ^3 isomers (**78**).

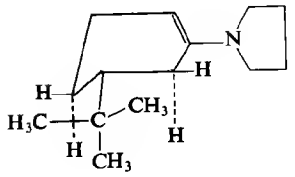


(**78**)

Interestingly the pyrrolidine enamine of 3-*t*-butylcyclohexanone (*41*) consists of a 3:2 mixture of Δ' and Δ^6 isomers (**79** and **80**). The preference for the Δ' isomer in this case is due to the relief of two of the four skew butane interactions, which are present in the Δ^6 isomer. The Δ' isomer, however, contains two additional interactions, i.e., one modified skew butane interaction ~0.4 kcal/mole (*42*) and one $A^{(1,2)}$ interaction between the C-2 vinylic hydrogen atom and the ethyl portion of the *t*-butyl group which is pointed toward it.

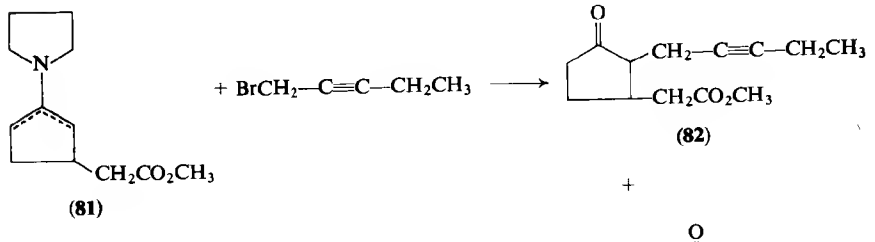


(79)



(80)

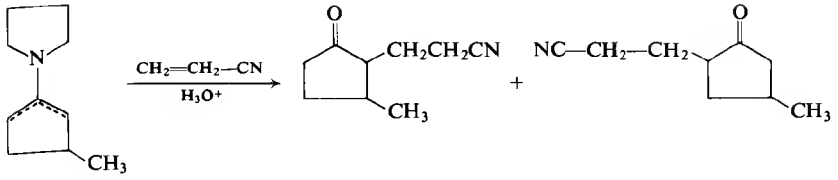
In the five-membered ring compounds, much less is known about the position of the double bond in the enamines of 3-alkyl ketones. Demole and Stoll (*43*) carried out the alkylation of the pyrrolidine enamine of methyl 1-oxo-3-cyclopentylacetate (**81**) with bromopentyne-2 to give a 4:5 mixture of C-2 and C-5 alkylated products (**82** and **83**).



(81) (82) (83)

The greater proportion of the 2,5-dialkyl product (**83**) is probably due to the presence of the larger amount of the Δ^5 isomer of the enamine, provided the alkylation of the Δ' isomer is not subject to any steric hindrance in the transition state and that there is no equilibration of enamines during the reaction.

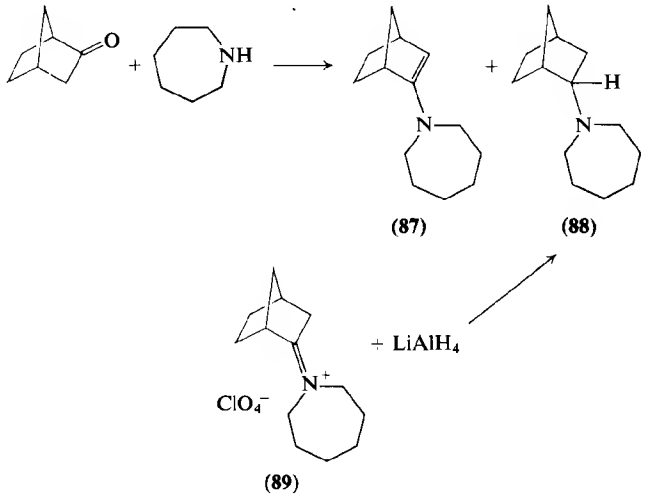
Lochte and Pitman (*44*) have reported the cyanoethylation of the pyrrolidine enamine of 3-methylcyclopentanone (**84**), the product being a mixture of C-2 and C-5 cyanoethylated ketones (**85** and **86**). Hunig and Salzwedel (*20*) have obtained a mixture of C_2- and C_5-acylated products from the reaction of morpholine enamine of 3-methylcyclopentanone with propionyl chloride.



(84) (85) (86)

C. ENAMINES OF BICYCLIC KETONES

Cook et al. (*45*) have studied the structure of the enamines of bicyclic ketones such as norbornanone. Acid-catalyzed condensation of norbornane with hexamethylenimine led to a 1:1 mixture of the corresponding enamine (**87**) and its dihydro derivative (**88**),

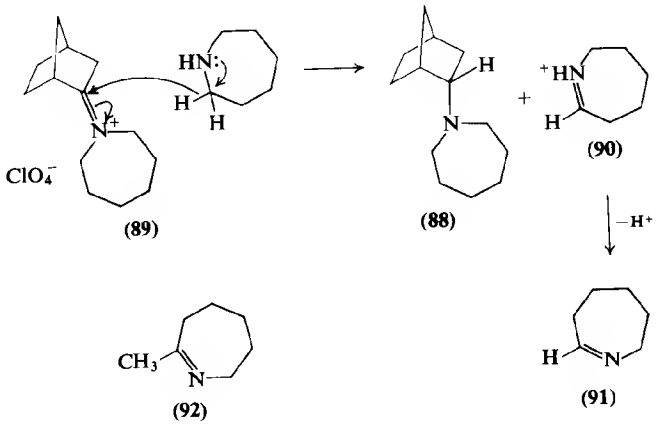


(87) (88) (89)

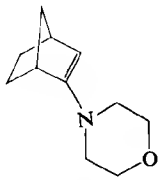
The saturated amine (**88**) was separated from the enamine (**87**) by basic hydrolysis, which resulted in the hydrolysis of the enamine. The perchlorate salt of the enamine (**89**) showed a strong absorption in the infrared at 1680 cm^{-1} (characteristic of

grouping) (*46*) and on treatment with lithium aluminum hydride was reduced to the saturated amine (**88**).

The formation of **88** is postulated to be occurring by the nucleophilic attack of a hydride ion (*47*), abstracted from the secondary amine, on the α-carbon atom of the iminium salt (**89**). The resulting carbonium ion (**90**) then loses a proton to give the imine (**91**), which could not be separated because of its instability (*48*). In the case of 2-methylhexamethylenimine, however, the corresponding dehydro compound Δ'-2-methylazacycloheptene (**92**) was isolated. The hydride addition to the iminium ion occurs from the less hindered exo side.

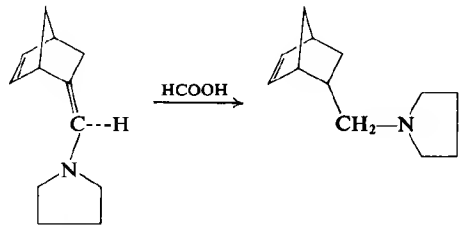


Other secondary amines such as pyrrolidine, di-*n*-butylamine, tetrahydroquinoline, *n*-benzylamine, and piperidine were also found to be capable of effecting this reduction. Interestingly, morpholine does not reduce enamines as readily (*47*) and its acid-catalyzed reaction with norbornanone was reported (*45*) to give only the corresponding enamine (**93**), although trace amounts of the reduction product were detected when cyclohexanone was treated with morpholine under these conditions (*47a*). The yield of morpholine reduction product was increased by using higher temperatures.



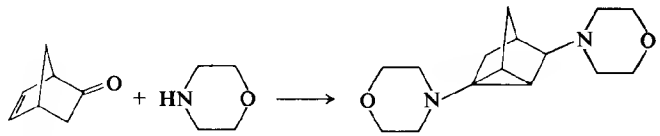
(93)

Another interesting fact to be noted is that the bicyclic enamine (**87**) and its pyrrolidine analogue failed to undergo reduction with 98% formic acid, whereas the pyrrolidine enamine of 2-bicyclo[2.2.1]hepten-5-carboxaldehyde (**94**), which exists largely in the transoid form (*49*), was readily reduced to (**95**). However, the saturated amine-substituted norbornane can be obtained directly from norbornanone under the more vigorous conditions of the Leuckart reaction (*49a*).



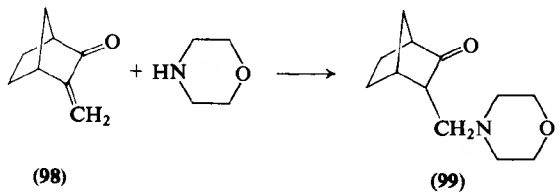
(94) (95)

Reaction of norbornenone (**96**) with morpholine led to the tricyclenamine (**97**) in 23% yield.



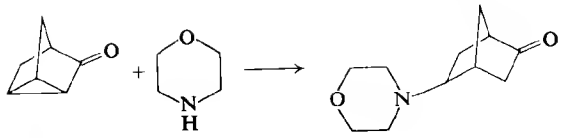
(96) (97)

The reaction of morpholine with 3-methylenebicyclo[2.2.1]heptan-2-one (**98**) gave the saturated ketone (**99**) as the only isolable product in 42% yield.



(98) (99)

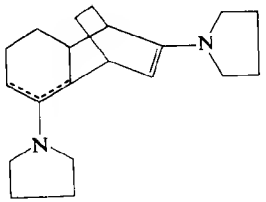
Interestingly, the reaction of tricyclenone (**100**) with morpholine also led to the exo isomer of the saturated ketone (**101**), involving the cleavage of the cyclopropane ring.



(100) (101)

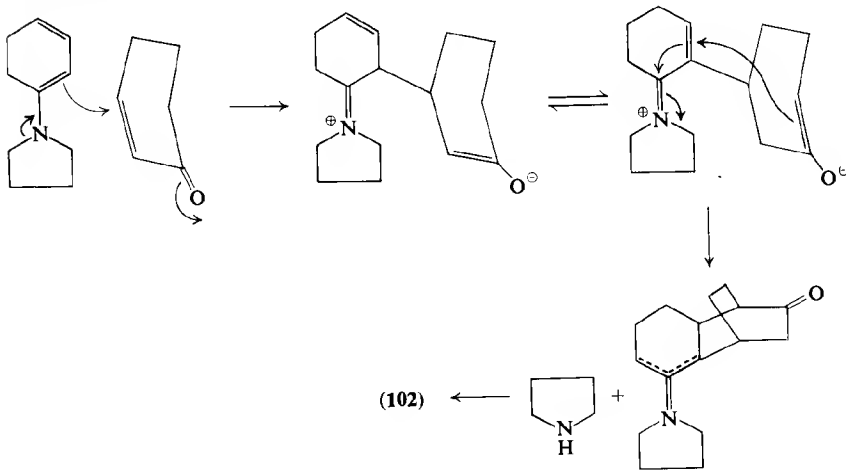
D. Enamines of α,β-Unsaturated Ketones

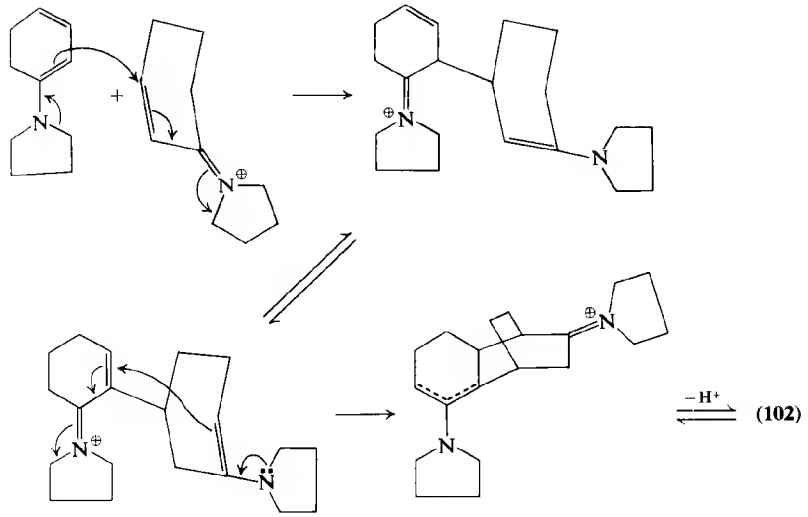
Leonard and Musliner (*50*) found that the reaction of 2-cyclohexenone with pyrrolidine in the presence of *p*-toluenesulfonic acid led to the dimeric enamine (**102**).



(102)

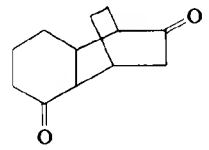
The following mechanistic pathways were proposed for the formation of this dimer.





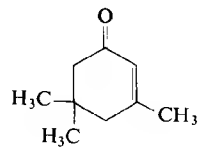
(102)

Hydrolysis of **102** gave the tricyclic ketone (**103**).

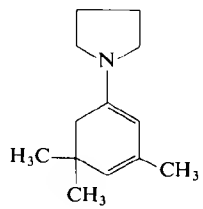


(103)

Substituted Δ^2-cyclohexenones such as 3,5,5-trimethyl-2-cyclohexenone (**104**) gave with pyrrolidine the corresponding enamine (**105**) (*50a*).

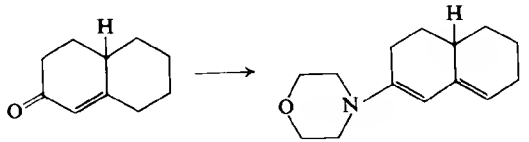


(104)



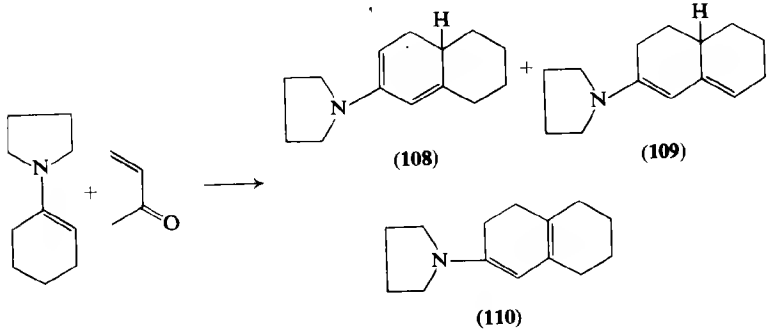
(105)

Bicyclic α,β-unsaturated ketones, e.g., $\Delta^{1(9)}$-2-octalone (**106**), give the corresponding heteroannular dienamines (**107**), as shown by UV spectroscopy, $\lambda_{max}^{Et_2O} = 270$ mμ, $\epsilon = 13{,}000$ (*51*). The preparation of this



(**106**) (**107**)

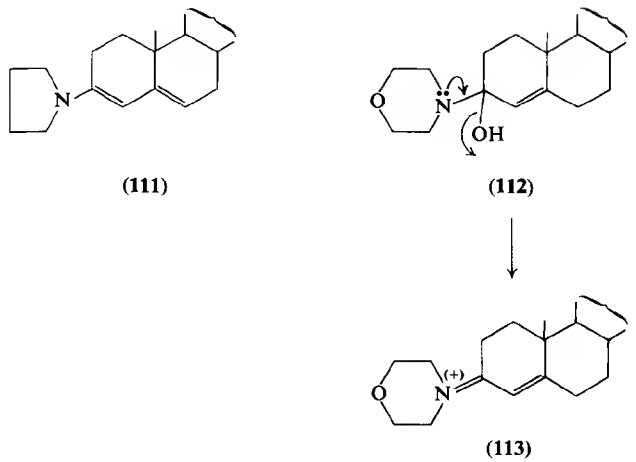
dienamine by the condensation of the enamine of cyclohexanone with methyl vinyl ketone, however, gave a mixture of homoannular and heteroannular dienamines (*52*). The product from the pyrrolidine enamine of cyclohexanone and methyl vinyl ketone was shown by NMR spectroscopy to be a mixture of 30% of (**108**), 65–70% of (**109**), and probably 5% of (**110**).



(**108**) (**109**) (**110**)

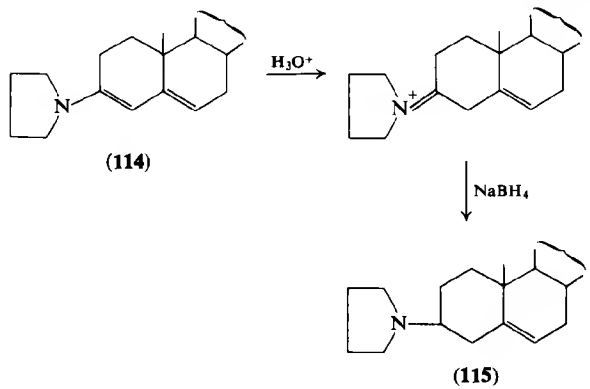
Steroidal α,β-unsaturated ketones such as Δ^4-3-ketones undergo a facile reaction with pyrrolidine to give the corresponding $\Delta^{3,5}$-dienamines (**111**) (*40,53*). The reaction is much slower with morpholine and piperidine, which is undoubtedly due to the generation of the double bond exocyclic to the six-membered hetero rings in the step involving the dehydration of the intermediate carbinolamine (**112**) to the corresponding iminium ion (**113**).

By analogy with the kinetic protonation of steroidal $\Delta^{3,5}$-enolate anions with weak acids such as acetic acid, which proceeds at the C-4 atom, since the maximum negative charge resides at this position (*54,55*), the kinetic protonation of the $\Delta^{3,5}$-dienamines with weak acids also occurs at this



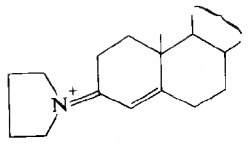
(**111**) (**112**) (**113**)

position. Marshall and Johnson (*56*) have reported that the reduction of the pyrrolidine enamine of Δ^4-3-cholestenone (**114**) and of 3,4-dehydroconnesine (**115**) with sodium borohydride and acetic acid resulted in the saturation of the Δ^3 double bond. The mechanism proposed for this reduction involves the protonation of the dienamine (**114**) at C-4 to give an iminium cation, which is then attacked by hydride at C-3 to give the amine (**115**).



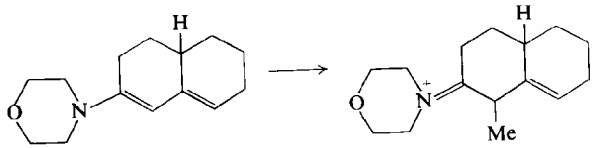
(**114**) (**115**)

Protonation with strong acids such as hydrochloric acid and hydrobromic acids occurs, however, at the 6 position (*53*) to give the thermodynamically more stable Δ^4-iminium salt (**116**), as shown by UV spectroscopy, $\lambda_{max}^{Et_2O} = 274$–$278$ mμ.

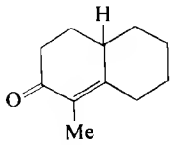


(116)

Another analogy between the enolate anions derived from α,β-unsaturated ketones and the corresponding enamines is encountered in their alkylation reactions (*57*), which proceed by the kinetically controlled attack at the α-carbon atom. For instance, Stork and Birnbaum (*51*) found that the alkylation of the morpholine enamine of $\Delta^{1(9)}$-octalone-2 (**117**) with methyl iodide gave the C-1 methylated derivative (**118**).

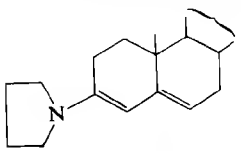


(117)

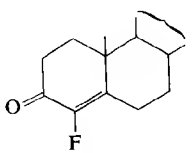


(118)

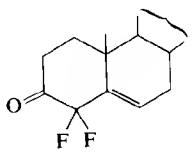
The pyrrolidine enamines of Δ^4-3-ketosteroids (**111**), on alkylation with methyl iodide, gave mainly the N-alkylated product (*3,53*) in nonpolar solvents such as benzene. The reaction in more polar solvents gave the 4-methylated product (*58*). The reaction of (**111**) with perchloryl fluoride involves attack at the C-4 atom to give, after acid hydrolysis, either 4-fluoro-Δ^4-3-ketone (**119**) or 4,4-difluoro-Δ^5-3-ketone (**120**), depending on the reaction conditions (*59*).



(111)



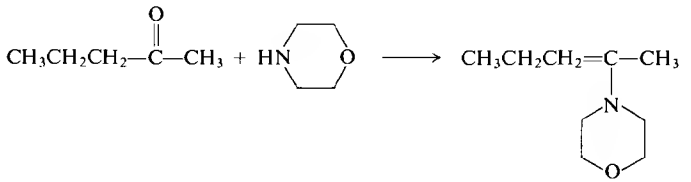
(119)



(120)

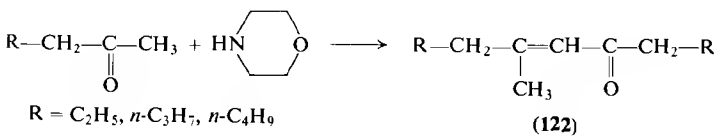
E. Enamines of Acyclic Ketones

Munk and Kim (*60*) have reported the preparation of the enamines of several acyclic ketones by refluxing the ketone with the amine for 66 hr to 76 days. For example the morpholine enamine of 2-pentanone was found to consist only of **121**.



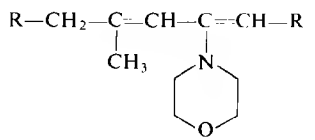
(121)

Madsen and Lawesson (*61*), however, have reported recently that the treatment of *n*-alkyl methyl ketones with morpholine in the presence of *p*-toluenesulfonic acid for a short period of time resulted in the formation of a mixture of condensation product of the ketone (**122**) and the corresponding dienamine (**123**).



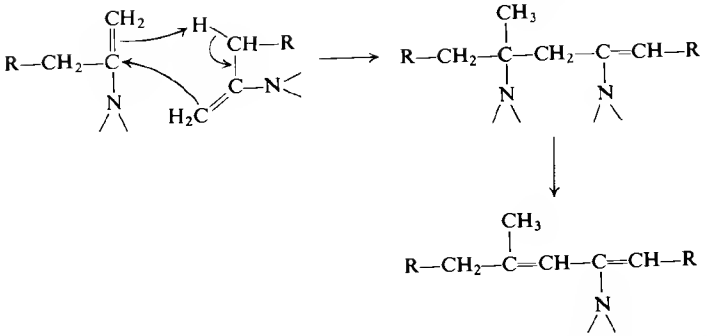
R = C_2H_5, *n*-C_3H_7, *n*-C_4H_9

(122)

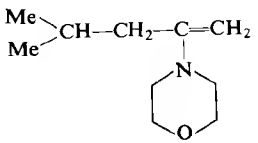


(123)

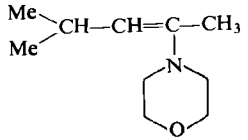
Similar results were encountered by Bianchetti et al. (*62*), who found that the ketal derivatives of *n*-alkyl methyl ketones with morpholine led to the enamines of the condensation products of these ketones. The authors have suggested the following probable mechanism for the dienamine formation.



Treatment of the diethylketal of methyl isobutyryl ketone with morpholine did not give the above condensation product (*63*), but led to a mixture of di- and tetrasubstituted isomers (**124** and **125**).

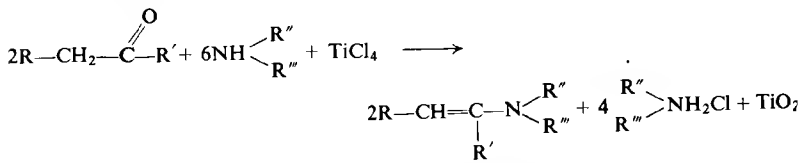


(**124**)

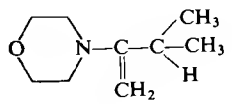


(**125**)

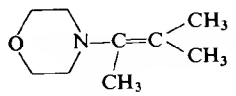
White and Weingarton (*64*) have recently described a novel method for the preparation of the enamines of the hindered ketones. The method involves the treatment of the ketone with an excess of the amine and a Lewis acid such as $TiCl_4$.



Morpholine enamine of methyl isopropyl ketone prepared by this method was found to be a 3:7 mixture of di- and tetrasubstituted isomers (**126** and **127**).

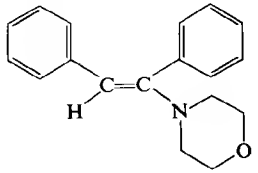


(**126**)



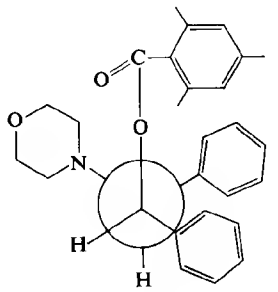
(**127**)

Munk and Kim (*65*) have shown that the acid-catalyzed condensation of desoxybenzoin with morpholine led only to the thermodynamically more stable *cis* isomer of the corresponding enamine (**128**).

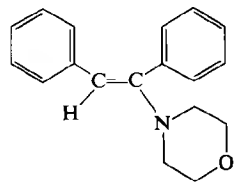


(**128**)

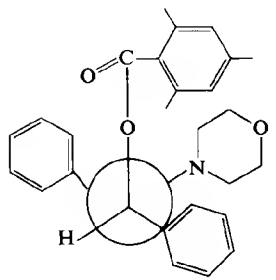
The stereochemical assignment is based on the comparison of the product with the pure *cis* and *trans* isomers (**128** and **129**) of the enamine prepared by the base-catalyzed climination of the mesitoate esters of the *dl*-erythro-2-(4-morpholino)-1,2-diphenylethanol (**130**) and the *dl*-threo-2-(4-morpholino)-1,2-diphenylethanol (**131**).



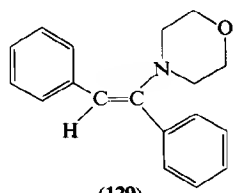
(**130**)



(**128**)

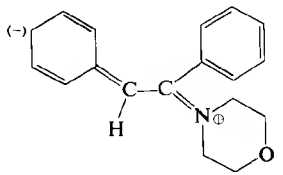


(**131**)



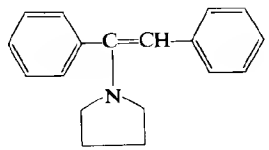
(**129**)

The *trans* isomer (**129**) underwent a facile isomerization in methanol to give an 88:12 mixture of the *cis* and *trans* isomers, showing that the difference in the free energy between them is of the order of 1.2 kcal/mole. The stability of the *cis* isomer may be ascribed to the continuous overlap between the electron pair on the nitrogen atom and the phenyl group, as shown in the resonance form (**132**).



(**132**)

Dulou et al. (*66*) have assigned the *trans* configuration to the pyrrolidine enamine of desoxybenzoin (**133**) on the basis of the comparison of its UV spectrum with that of *trans*-stilbene and triphenylethylene. This assignment is open to question in the light of the work of Munk and Kim (*65*).



(**133**)

III. Physical Properties of Enamines

A. Infrared Spectra

In the IR spectra of the enamines the double bond stretching appears as a strong band at 1630–1660 cm^{-1} (*67,68*). The high extinction coefficient for this absorption may be attributed to the overlap between the electron pair on the nitrogen atom and the π electrons of the double bond. Gurowitz and Joseph (*69*) have found that the trisubstituted isomer of the morpholine enamine of 2-methylcyclohexanone exhibits a strong band at 1650 cm^{-1}, whereas the corresponding tetrasubstituted isomer shows an extremely weak band at 1675 cm^{-1}, which is undoubtedly a reflection of the low degree of the electronic overlap in the latter case.

A hypsochromic shift of 20–50 cm^{-1} is observed in the double-bond stretching region, when the enamines are converted to the corresponding iminium salts by the electrophilic addition of a proton at the β-carbon atom. The shift is accompanied by an enhancement in the intensity of the band. Leonard and co-workers (*68,71–74*) have used this absorption shift as a diagnostic tool for the determination of the position of the double bond

with respect to the nitrogen atom. Some of the examples exhibiting this characteristic shift are listed in Table 2.

TABLE 2

Double-Bond Stretching Frequencies of Enamines and Their Perchlorate Salts

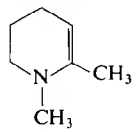
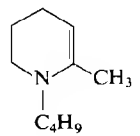
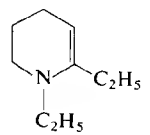
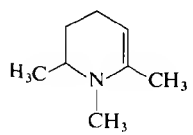
Compound	ν_{max} of enamine, cm^{-1} (liquid film)	ν_{max} of salt, cm^{-1} (Nujol)	Ref.
	1650	1686	*68,70*
	1649	1684	*68*
	1646	1671	*71*
	1652	1697	*71*

TABLE 2—cont.

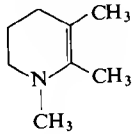
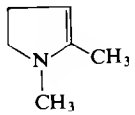
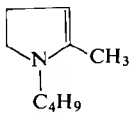
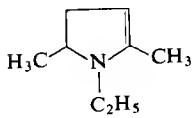
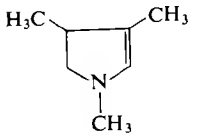
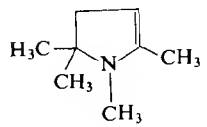
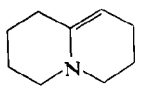
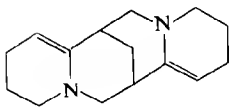
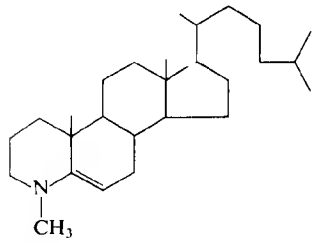
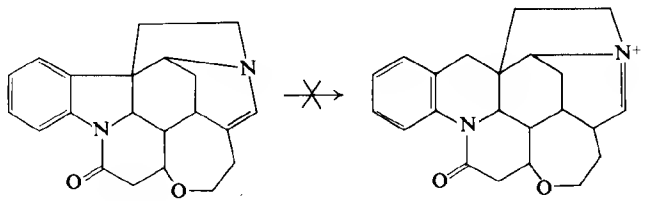
Compound	ν_{max} of enamine, cm^{-1} (liquid film)	ν_{max} of salt, cm^{-1} (Nujol)	Ref.
	1657	1682	*71*
	1640	1701	*72*
	1639	1685	*68*
	1644	1678	*72*
	1648	1693	*72*
	1635	1677	*72*
	1652	1696	*73*
	1645	1690	*74*

TABLE 2—cont.

Compound	ν_{max} of enamine, cm^{-1} (liquid film)	ν_{max} of salt, cm^{-1} (Nujol)	Ref.
	1634	1654	*75*

The enamines in which the protonation at the β-carbon atom is not allowed due to the lack of coplanarity, or, in other words, the lack of electronic overlap, do not exhibit this characteristic absorption shift. For instance in the case of neostrychnine (**134**) where the overlap is not permitted since this would involve the formation of a double bond at the bridgehead, there is no appreciable difference in the C=C stretching region of the free amine and its perchlorate salt; they absorb at 1666 cm^{-1} and 1665 cm^{-1}, respectively (*70*).



(134)

The IR spectra of several enaminoketones have been reported, and a study of these spectra has shown strong coupling between the C=O and C=C stretching vibrations and band splitting due to rotational isomerism (*75a,75b*).

B. Ultraviolet Spectra

The introduction of a double bond in conjugation with the nitrogen atom results in a bathochromic shift. For instance, in contrast with the saturated amines ($\lambda_{max} - 215$ mμ; $\epsilon - 3000$), the enamines show a maximum at

230 ± 10 mμ with a hyperchromic effect on the extinction coefficient (5000–9000) (*76*). These changes may be ascribed to the overlap between the electron pair on the nitrogen atom and the π electrons on the double bond. The heteroannular dienamines (*40,53*) derived from the α,β-unsaturated ketones show maxima at 270–280 mμ ($\epsilon = 19{,}000$–$26{,}000$). In Table 3, some examples of the UV maxima of the enamines are given. Theoretical calculations of the electronic structures and spectral properties of enamines and dienamines have been made (*76a*).

TABLE 3

UV Maxima of Enamines

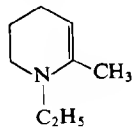
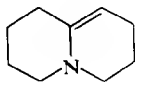
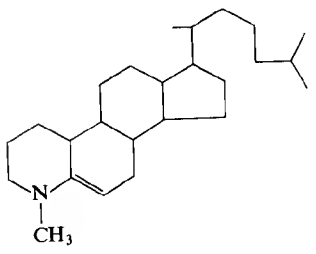
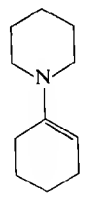
Enamine	λ_{max}, mμ	ϵ_{max}	Ref.
	231	5,100	*76*
	228	5,600	*76*
	221	8,800	*75*
	224.5	8,300	*67*

TABLE 3—cont.

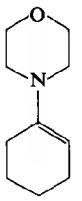
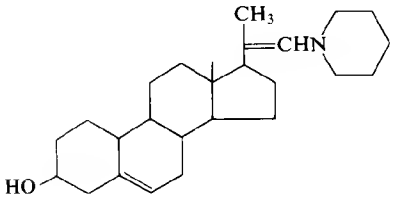
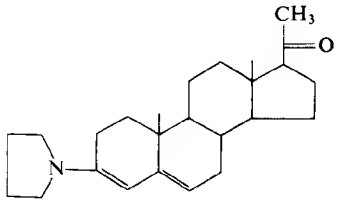
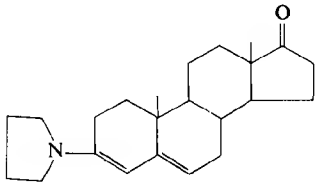
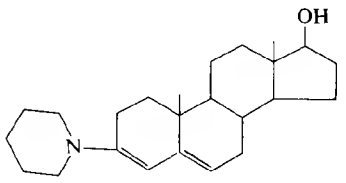
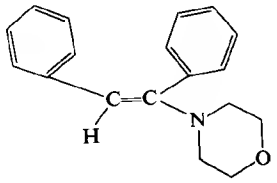
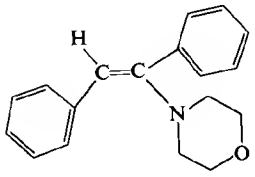
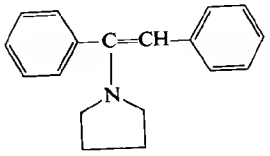
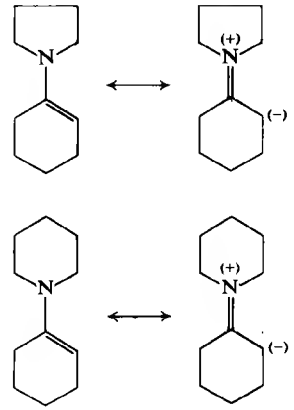
Enamine	λ_{max}, mμ	ϵ_{max}	Ref.
	222.5	7,900	*67*
	235	7,355	*77*
	281	22,725	*53*
	281	23,000	*53*
	281	23,000	*53*

TABLE 3—cont.

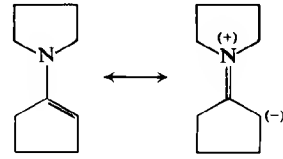
Enamine	λ_{max}, mμ	ϵ_{max}	Ref.
	224 306	14,800 11,600	*65*
	240 320	14,600 11,400	*65*
	227 312	12,500 18,900	*66*

C. Nuclear Magnetic Resonance Spectra

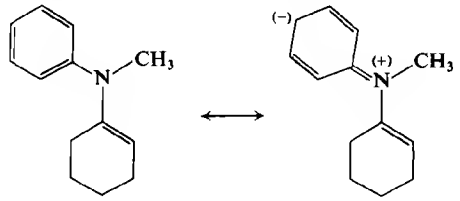
In the NMR spectra of the enamines the position of the vinylic proton is indicative of the degree of overlap between the electron pair on the nitrogen atom and the double bond (*13,15*). The greater the overlap, the higher is the field at which this proton appears. For instance in case of the pyrrolidine enamine of cyclohexanone, in which the double bond is exocyclic to one five-membered ring and one six-membered ring, the vinylic proton appears at 250 Hz, whereas in case of the corresponding morpholine and piperidine enamines, in which the double bond is exocyclic to two six-membered rings—a less favored situation—the vinylic proton appears at a lower field, i.e., at 273–277 Hz.



The pyrrolidine enamine of cyclopentanone, in which the double bond is exocyclic to two five-membered rings, shows the vinylic proton at 237 Hz (*78*).



In the NMR spectrum of the N-methylaniline enamine of cyclohexanone (**135**), the vinylic proton appears at a much lower field, i.e., at 324 Hz (*15*). Here the electron pair on nitrogen tends to conjugate with the phenyl group thus exhibiting a very small degree of overlap with the enamine double bond.



(135)

The chemical shifts for the vinylic protons of some enamines are given in Table 4.

TABLE 4

The Chemical Shifts of Vinylic Protons of Enamines

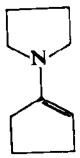
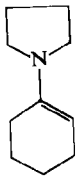
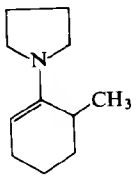
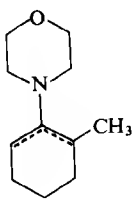
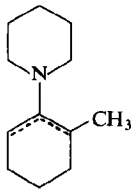
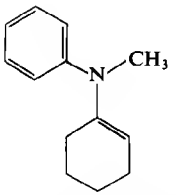
Enamine	Chemical shift, Hz[a]	Ref.
	237	*78*
	250	*13*
	251	*13*
	273	*13*
	276	*13*

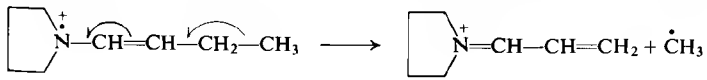
TABLE 4

Enamine	Chemical shift, Hz[a]	Ref.
	277	*13*
	324	*4,15*

[a] Downfield from tetramethylsilane.

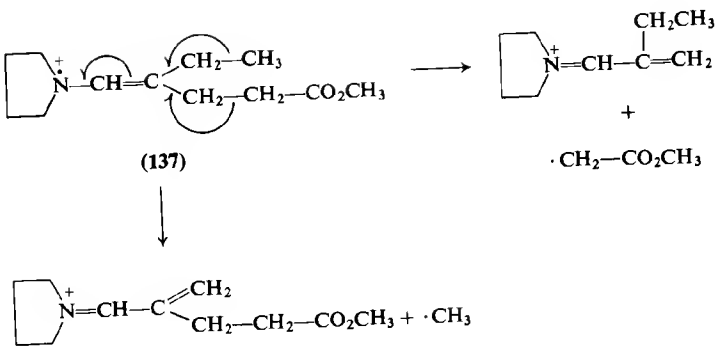
D. Mass Spectra

The mass spectra of the enamines have been studied in detail by Williams et al. (*16*). The spectra of these compounds can be interpreted in terms of charge localization on the nitrogen atom in the molecular ions, which may undergo fragmentation at the position alpha to the double bond, giving fragments with an increased conjugation. In this step the loss of the hydrogen radical is less favored than that of the alkyl radical. For instance, the pyrrolidine enamine of butyraldehyde (**136**) has a base peak at *m/e* 110, formed by the loss of the methyl radical. The nature of branching in the aldehydes may also be elucidated by the mass spectra of their enamines. This is illustrated by the mass spectrum of the pyrrolidine enamine of



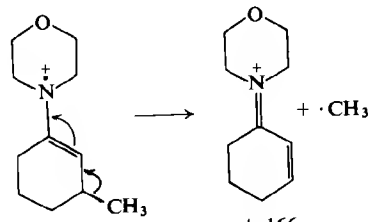
(**136**) *m/e* 110

2-(2-carbomethoxyethyl)butyraldehyde (**137**). In this case the most abundant fragment ions are formed by the ejection of the resonance stabilized carbomethoxymethyl radical and methyl radical.

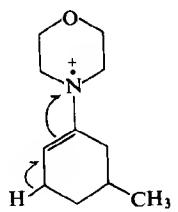


(137)

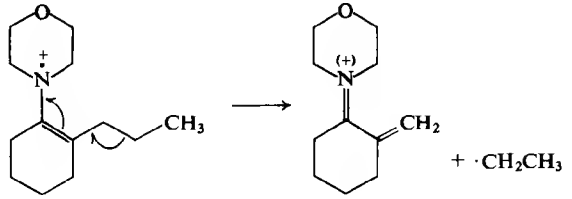
Information regarding the position of the substituents can be obtained from the mass spectra of the enamines of cyclic ketones. For instance in the case of the morpholine enamine of 3-methylcyclohexanone, which is shown to be a 2:1 mixture of Δ' and Δ^6 isomers by NMR spectroscopy, the fragmentation of the radical ion from the Δ' isomer results in the loss of a methyl radical from the C-3 position. The Δ^6 isomer gives a complicated spectrum due to the loss of the hydrogen radical.



m/e 166



Another interesting example is found in the morpholinc enamine of 2-*n*-propylcyclohexanone (**138**), which consists of a 2:3 mixture of tri- and tetrasubstituted isomers. The radical ion from the tetrasubstituted isomer loses an ethyl radical, giving the base peak at *m/e* 180.



(138)

E. Basicity

Enamines possessing a primary or a secondary nitrogen atom are less basic than the corresponding saturated amines (*79*). On the other hand many enamines with a tertiary nitrogen atom have been shown to be more basic in aqueous solution. This has been attributed to the fact that the resulting quaternary hydroxide is a stronger base than the saturated analogues (*72,74,80* and *81*). However, the generality of increased basicity in a tertiary amine due to the presence of an α,β double bond has been strongly questioned (*81a*). Rather, it is argued that the presence or absence of α- or β-alkyl substituents in the enamine is the important determining factor, α-alkyl substituents being base strengthening and β-alkyl substituents being base weakening. (See Section F for Hückel calculations of the electron density at the β-carbon, the protonating carbon, for both the α- and β-alkyl-substituted enamines.)

This apparent characteristic enhancement in the basicity has been used quite frequently for the determination of the position of a double bond with respect to the nitrogen atom in unsaturated amines. The cases such as neostrychnine (**134**) and dehydroquinuclidine (**139**) in which the protonation at the β-carbon atom cannot occur due to the lack of overlap between the electron pair on the nitrogen atom and the π electrons of the double bond, since this would involve the formation of a double bond at the bridgehead—a violation of Bredt's rule—show a decrease in basicity. For instance the basicities of quinuclidine (**140**) and dehydroquinuclidine (**139**) have been shown by Grob et al. (*82*), to differ by 1.13 pK units in aqueous solution at 25°. This decrease in basicity has been attributed to the electron-withdrawing inductive effect of the double bond.

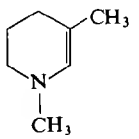
(139)

(140)

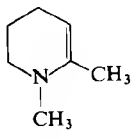
Recently Stamhuis et al. (*83*) have determined the base strengths of morpholine, piperidine, and pyrrolidine enamines of isobutyraldehyde in aqueous solutions by kinetic, potentiometric, and spectroscopic methods at 25° and found that these enamines are 200–1000 times weaker bases than the secondary amines from which they are formed and 30–200 times less basic than the corresponding saturated tertiary enamines. The base-weakening effect has been attributed to the electron-withdrawing inductive effect of the double bond and the overlap of the electron pair on the nitrogen atom with the π electrons of the double bond. It was pointed out that the kinetic protonation in the hydrolysis of these enamines occurs at the nitrogen atom, whereas the protonation under thermodynamic control takes place at the β-carbon atom, which is, however, dependent upon the pH of the solution (*84,85*). The measurement of base strengths of enamines in chloroform solution show that they are 10–30 times weaker bases than the secondary amines from which they are derived (*4,86*).

F. Gas–Liquid Chromatography and Hückel LCAO MO Calculations

The separation of mixtures involving N-methyl-Δ^2-tetrahydropyridines into their pure components by means of gas–liquid chromatography was discussed in a report by Holík et al. (*87*). They found that, using tris(β-cyanoethoxymethyl)-γ-picoline as the stationary phase, the primary factors involved in the specific retention volumes of these enamines is the electronic effect of a methyl substituent and the nitrogen atom on the carbon–carbon double bond. It was observed that 1,3-dimethyl-Δ^2-tetrahydropyridine (**141**) has a smaller specific retention volume and, hence, is eluted before

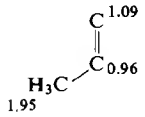


(141)

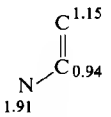


(142)

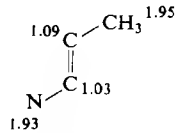
1,2-dimethyl-Δ^2-tetrahydropyridine (**142**), which has a larger specific retention volume. Hückel LCAO MO calculations showed the distribution of electron densities in model alkene and enamine structures as follows (*87,76a*):



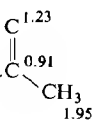
(143)



(144)



(145)



(146)

These calculations indicate that both the methyl group and the nitrogen atom increase the electron density around the carbon atom in the double bond which is β to the substituent (models **143** and **144**). Therefore, when both of these groups are bonded to the same carbon atom of the double bond, this increase of electron density about the β-carbon atom is intensified (as in model **146** and compound **142**). This type of compound, then, is more strongly held by the stationary phase, and hence its retention time is longer than that of compound **141**, where the effects of the methyl substituent and the nitrogen counteract each other (model **145**).

ACKNOWLEDGMENT

The author wishes to thank Dr. F. Johnson for helpful discussion in the preparation of this chapter.

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2

METHODS AND MECHANISMS OF ENAMINE FORMATION

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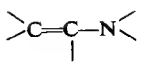
I. Introduction

The primary objectives of this chapter are to detail the methods by which enamines (α,β-unsaturated amines) (**1**) can be synthesized and the mechanisms of enamine formation. The enamines discussed are those in which the nitrogen is tertiary and, with the exception of a few selected examples, contain no other functional groups. The term "simple enamines" might be used to describe the majority of enamines noted in this chapter.

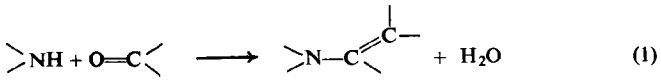


(1)

II. Enamines from the Condensation of Aldehydes and Ketones with Secondary Amines

A. General Aspects

The most versatile method for preparing enamines involves the condensation of aldehydes and ketones with secondary amines [Eq. (1)]. Mannich and Davidsen (*1*) discovered that the reaction of secondary amines with aldehydes in the presence of potassium carbonate and at temperatures near 0° gave enamines, while calcium oxide and elevated temperatures were required to cause a reaction between ketones and secondary amines, although usually in poor yield. The introduction by Herr and Heyl (*2–4*) of the removal of the water produced in the condensation by azeotropic distillation with benzene made possible the facile preparation of enamines from ketones and disubstituted aldehydes.



(1)

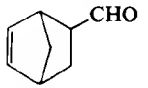
This innovation was exploited by Stork and his co-workers (*6–8*) for a study of enamine formation from a variety of ketones and secondary amines.

A number of modifications of this general method have been published. The benzene may be replaced by toluene or xylene to give a reasonable rate of reaction (*9,10*). An acid catalyst, *p*-toluenesulfonic acid (*3,4*), Dowex-50 (*11*), montmorillonite catalyst KlO (*12*), or even acetic acid (*13*) can be employed for the normal condensations or when the uncatalyzed reaction is slow. As an alternative to removal of the water by means of a water separator, the water can be removed by passing the condensate through a drying agent such as calcium carbide (*14*) or a molecular sieve (*15,16*). By replacing the normally employed potassium carbonate or calcium oxide (*1*) by granular calcium chloride, Blanchard (*17*) was able to synthesize the N,N-dimethyl- and N,N-diethylenamines of cyclopentanone and cyclohexanone in greater than 50% yields. The procedure simply involves stirring at room temperature a mixture of the ketone, the amine (in excess), and calcium chloride in ether. Barium oxide has also been used (*18*) to

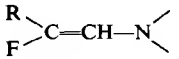
replace potassium carbonate or calcium oxide. Methanol, acetone, pyridine, or dimethylformamide may be used as solvents for the preparation of the pyrrolidinyl enamines of the Δ^4-3-ketosteroids (*14*).

The condensation of aldehydes with secondary amines has also received considerable attention since the original work of Mannich and Davidsen (*1*). In their study to extend the scope of the Leuckart–Wallach reaction (the reductive alkylation of amines by aldehydes, usually formaldehyde, and ketones in the presence of formic acid), deBenneville and Macartney (*19*) synthesized a number of enamines derived from both aliphatic and aromatic aldehydes and several secondary amines. Herr and Heyl (*2*) first introduced their azeotropic procedure for the preparation of the piperidyl and morpholinyl enamines of steroidal aldehydes. Instead of using benzene or similar solvents to form water azeotropes, Benzing (*20,21*) used excess isobutyraldehyde in the preparation of enamines from this aldehyde. That enamines of aldehydes and dimethylamine can successfully be formed under quite different operating conditions is illustrated by two syntheses using xylene as the solvent. One preparation requires potassium hydroxide and a temperature of −15°, while acetaldehyde is added and then a temperature of 20° for 20 hr (*22*). The other (*23*) makes use of an autoclave containing the aldehyde, potassium carbonate, dimethylamine, and xylene which is rocked for 4 hr at 100°. N,N-Dimethylpropenylamine has been prepared by adding propionaldehyde to a mixture of anhydrous dimethylamine, ether, and Linde No. 13X molecular sieve (*24*).

The next seven references are cited not because of the experimental procedures described but because they indicate diversification in the types of enamines prepared and studied. Both Paquette (*25*) and Kasper (*26*) have condensed 2,5-methylene-1,2,5,6-tetrahydrobenzaldehyde (5-norbornene-2-carboxyaldehyde) (2) with several cyclic and open-chain aliphatic secondary amines. Kasper studied the ratio of endo to exo aldehyde formed upon hydrolysis of these enamines and the dihydro enamines. Paquette investigated the addition of sulfene to the enamines. β-Fluoro-



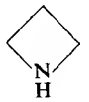
(2)



(3)

enamines (**3**), which hydrolyze less readily than corresponding simple enamines, have been prepared from α-fluoroaldehydes and piperidine, pyrrolidine, and morpholine (*27*).

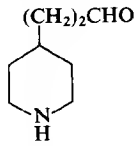
The secondary amines used in the preparation of enamines have been primarily simple dialkylamines or cyclic amines of five- or higher-membered rings. Azetidine (**4**) yields a stable enamine with cyclopentanone (*28*). No simple enamines formed by condensation of ethylenimine (**5**) or a substituted ethylenimine with an aldehyde or ketone have been reported.



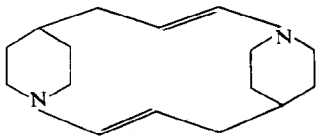
(**4**)

(**5**)

Osmotic pressure measurements and the NMR spectra of dilute solutions of the aminoaldehyde (**6**) indicated that the primary species in solution was the dimeric enamine (**7**) (*29*).

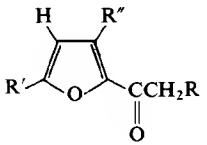


(**6**)

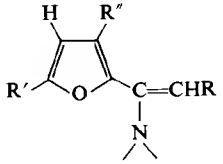


(**7**)

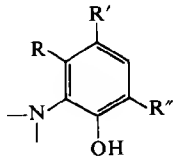
An interesting preparation of substituted *o*-aminophenols has been developed by Birkofer and Daum (*30*). 2-Acylfurans (**8**) plus an aliphatic secondary amine presumably condense to give the corresponding enamine (**9**) (not isolated), which undergoes thermal isomerization to the *o*-aminophenol (**10**).



(**8**)

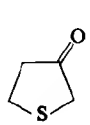


(**9**)

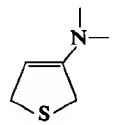


(**10**)

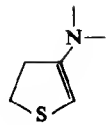
The cyclic thioketone, 3-oxotetrahydrothiophene (**11**), gives a mixture of enamines (**12**,**13**) when caused to react with a secondary amine such as piperidine or pyrrolidine (*31*). The enamine mixture can be reduced to the 3-aminotetrahydrothiophene using formic acid or oxidized to the 3-aminothiophene using diisopentylsulfide.



(**11**)

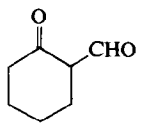


(**12**)

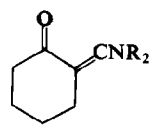


(**13**)

If a molecule contains both a ketonic and aldehydic carbonyl group, a secondary amine will react with the aldehydic carbonyl group to give a β-enamino ketone (**15**). This has been shown not only for 2-formylcyclohexanone (**14**) (*32*,*33*) but also in steroidal systems when the aldehyde and ketone groups are in five- or six-membered rings (*34*).



(**14**)



(**15**)

The following reference numbers, some of which have been cited previously, are good sources for lists of simple enamines, their physical properties, methods of preparation or references thereto, and yields: *1*, *9*, *18*, *19*, *24*, *35*, *36*, *36a*, and *37*. They provide a reasonable starting place for a research scientist who requires this kind of information.

B. Mechanistic and Structural Considerations

The overall reaction pathway usually presented (*1*,*9*,*19*,*36*) for the preparation of an enamine from an aldehyde bearing an α-hydrogen and a secondary amine is given in Eqs. (2) and (3). Intermediate **16**, which can be isolated in

$$\text{RCHCHO} + 2\text{HNR}_1\text{R}_2 \xrightarrow{-\text{H}_2\text{O}} \underset{\textbf{(16)}}{\text{RCHCH(NR}_1\text{R}_2)_2} \qquad (2)$$

$$\textbf{(16)} \xrightarrow{\Delta} \text{RC=CHNR}_1\text{R}_2 + \text{HNR}_1\text{R}_2 \qquad (3)$$

some cases (*1*,*27*,*38*,*39*), is called an aminal. Therefore most investigators have used at least a twofold molar excess of amine to convert the aldehyde to the enamine in good yield.

That an aminal is a necessary intermediate was first questioned by Herr and Heyl (*2*). They found that by using a slight excess of amine the yield of the enamine from two of the steroidal aldehydes studied was 84%. Also, the β-fluorocnamines discussed earlier are formed in 60–90% yield from equimolar amounts of the β-fluoroaldehyde and secondary cyclic amine (*27*). However, neither of these studies was specifically designed to show whether or not aminals were intermediates.

Experiments designed to clarify the situation were carried out by Wittig and Mayer (*40*). It was shown that changing the molar ratio of amine (diethylamine, di-*n*-butylamine, or diisobutylamine) to *n*-butyraldehyde from 1:1 to 2:1 did not affect the yield of enamine (53–64%, based on the aldehyde). Contrariwise, changing the ratio of amine (morpholine, piperidine, or pyrrolidine) to *n*-butyraldehyde from 1:1 to 2:1 boosted the yields from 52–57% to 80–85%. The authors interpret these data as indicating that the cyclic amines form aminals with *n*-butyraldehyde, while the open-chain do not. Infrared evidence is stated as having shown that the aminal originates not from attack of excess amine on the enamine, which is stable under the conditions of the reaction, but from the N-hemiacetal (**17**).

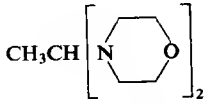
$CH_3CH_2CH_2CH(OH)(NR_2)$

(17)

The concession is made that longer reaction times, as used by Mannich and Davidsen (*1*), could produce an aminal from an enamine plus excess amine.

In contrast to Wittig and Mayer's results (*40*), ethylidenebisdimethylamine (1,1-bisdimethylaminoethane) has been prepared, albeit by a very different method [$AsN(CH_3)_2$ plus acetaldehyde in ether; see Section VII], and found to be distillable with only slight decomposition (*39*).

That aminals and enamines are in equilibrium under certain conditions has been demonstrated (*38*). 1,1-Di(N-morpholino)ethane **18**, when heated with excess diethylamine for 24 hr at 60° and then treated with 4-nitrophenylazide, gave the triazole (**19**) in 80% yield. The authors contend that



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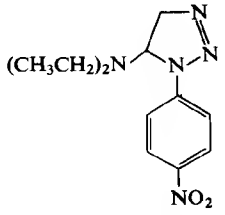
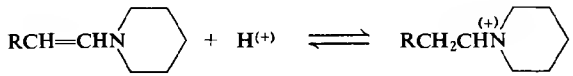


(19)

for this to occur the aminal (**18**) must be in equilibrium with N-vinylmorpholine, which is eventually converted to N-vinyldiethylamine.

Additional evidence that a dynamic equilibrium exists between an enamine, N-hemiacetal, and aminal has been presented by Marchese (*41*). It should bc noted that no acid catalysts were used in the reactions of aldehydes and amines discussed thus far. The piperidino enamine of 2-ethylhexanal (0.125 mole), morpholine (0.375 mole), and *p*-toluenesulfonic acid (1.25×10^{-4} mole) diluted with benzene to 500 ml were refluxed for 5 hr. At the end of this time the enamine mixture was analyzed by vapor-phase chromatography, which revealed that exchange of the amino residue had occurred in a ratio of eight morpholine to one piperidine. Marchese proposed a scheme [Eqs. (4), (5) and (6)] to account for these



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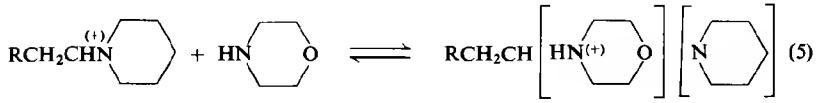

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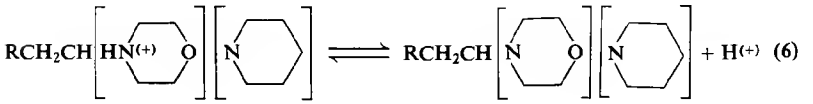


(6)

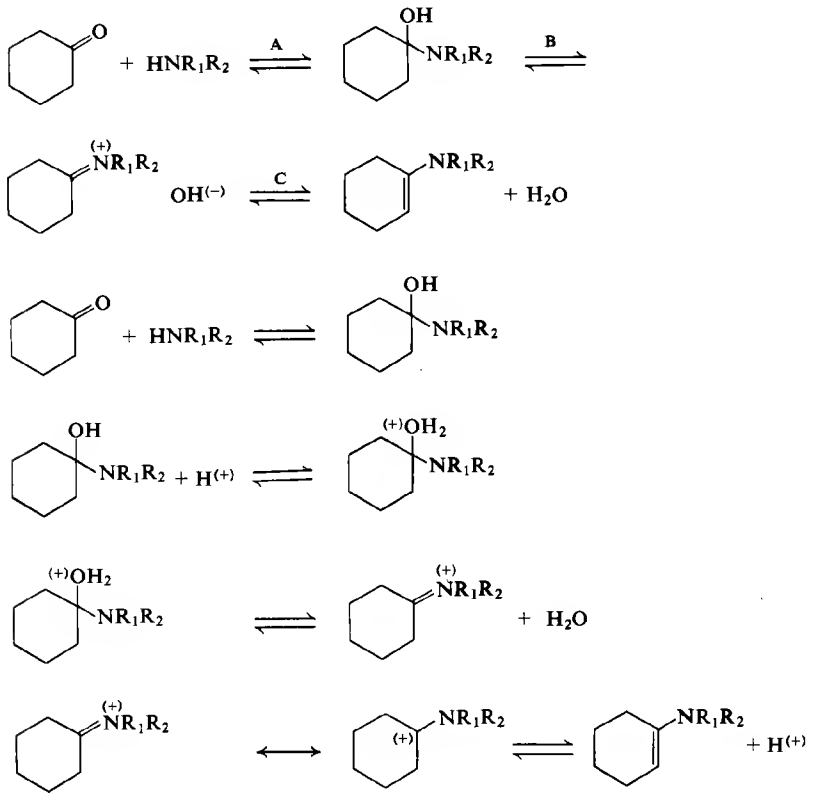
(20)

results. Either the aminal (**20**) could break down upon distillation to give the mixture of enamines or by a series of similar equilibrium steps the piperidine group could be protonated and eventually lost as piperidine.

Thc cvidence accumulated to date unfortunatcly is not conclusive. The most accurate statement which probably can be made is that aminals are produced when aldehydes and secondary amines react, but the aminals are not necessarily the direct precursor of the enamine.

The intermediacy of an aminal in the formation of enamines from ketones and secondary amines is not usually proposed. The only direct evidence for this is the infrared spectra of the reaction mixtures produced when dimethyl- or diethylamine was allowed to react with cyclohexanone or cyclopentanone

in ether (*17*). The spectra revealed the presence of the enamine double bond (1640 cm^{-1}) prior to distillative work-up. General mechanisms for the noncatalyzed (*9,42*) and acid-catalyzed reaction (*41*) have been offered.



The only kinetic data reported are in a Ph.D. thesis (*41*). Integral order kinetics were usually not obtained for the reaction of a number of ketones with piperidine and a number of secondary amines with cyclohexanone. A few of the combinations studied (cyclopentanone plus piperidine, pyrrolidine, and 4-methylpiperidine, and N-methylpiperazine plus cyclohexanone) gave reactions which were close to first-order in each reactant. Relative rates were based on the time at which a 50% yield of water was evolved. For the cyclohexanone–piperidine system the half-time ($t_{1/2}$) for the 3:1 ratio was 124 min and for the 1:3 ratio 121 min. It appears that an

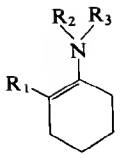
excess of ketone is just as effective as an excess of amine in driving the reaction to completion. The $t_{1/2}$ for the 1:1 ratio is 547 min. The conclusions drawn from the data in the thesis are similar to those of Stork and coworkers†:

> The rate is affected, not unexpectedly, by two factors: the basicity and steric environment of the secondary amino group and the nature and environment of the carbonyl group. Of the secondary amines used, pyrrolidine gives a higher reaction rate than the more weakly basic morpholine, while cyclic amines generally produce enamines faster than open-chain ones. This is of course what would be expected, but the fact that pyrrolidine reacts faster than piperidine may deserve comment. The basicity and steric environment of the two bases are closely similar (Pyrrolidine has $K = 1.3 \times 10^{-3}$, morpholine has $K = 2.44 \times 10^{-6}$, and piperidine has $K = 1.6 \times 10^{-3}$.) and the differences in rate are probably to be ascribed to the different rates of the dehydration steps: The transition state with pyrrolidine involves making a trigonal carbon in a five-membered ring and the faster rate of solvolysis of methylcyclopentyl chloride than that of the corresponding cyclohexyl compound (H. C. Brown, *J. Chem. Soc.*, **1956**, 1248) correlates with the faster formation of an enamine from pyrrolidine than from piperidine. The effect of the ring size in the case of cyclic ketones is also notable: cyclopentanone reacts most rapidly, followed by cyclohexanone which is faster than the seven- and higher-membered ketones. If the rate of formation of enamines were solely a reflection of the rate of formation of the intermediate carbinolamines, cyclohexanone would form its enamine faster than cyclopentanone. If, on the other hand, the rate of dehydration of the carbinolamine were the controlling factor, then the seven-membered ring would be faster than the six. Since neither of these orders corresponds to the experimental one, the over-all rate is evidently not solely ascribable to any single one of the reversible steps A, B and C involved in the formation of the enamine.

If cyclic ketones are monosubstituted in the α-position, their rates of reaction decrease as compared to the rate for the parent ketone (*9,41*). More highly substituted ketones (e.g., diisobutyl ketone, diisopropyl ketone) can be caused to react using newer preparative techniques (*39,43,44*; see Section VII). Monosubstituted acetones often can give self-condensation products, but the recent literature (*13,39,43*) contains reports of the successful formation of the enamines of methyl ketones.

The general rule has been formulated (*9*) that the less substituted enamine is formed from unsymmetrical ketones such as the 2-alkylcyclohexanones. In enamine **21** the R_1 group and the N-alkyl groups would interfere with one another if overlap is to be maintained between the nitrogen unshared electrons and the double bond. There would be less repulsion if the isomeric enamine (**22**) were formed. 2-Phenylcyclohexanone and pyrrolidine with *p*-toluenesulfonic acid as catalyst in refluxing benzene gave enamine

† Reprinted from Ref. 9, p. 209, by courtesy of the American Chemical Society.



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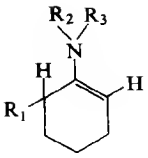
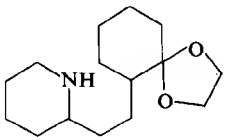


(22)

22 [$R_1 = C_6H_5$, R_2, $R_3 = (CH_2)_4$] (*45*). Even the possibility of stabilization of the double bond by conjugation with an aromatic ring was not enough to overcome the steric repulsions. The enamine formed is probably an equilibrium product (*46*).

When the acetal (**23**) is placed in 20% aqueous hydrochloric acid, then hydroxide, and finally refluxed in toluene, the enamines (**24,25**) are obtained in 86% yield and in a **4**:1 ratio of **24** to **25** (*47*). The ratio was determined



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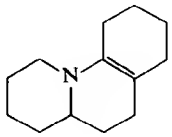

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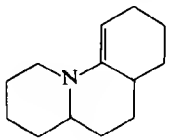


(25)

by NMR spectroscopy. The pyrrolidino analogue of **23** gives the corresponding enamines in a 6:4 ratio of tetrasubstituted to trisubstituted. That these ratios represent equilibrium mixtures was shown by refluxing the isomeric enamines in benzene containing *p*-toluenesulfonic acid. The same ratios were noted. The isomeric enamines could not be separated by vapor-phase chromatography. These results support the conclusion that steric interference is the chief cause of the formation of the less substituted enamine from unsymmetrical ketones, for when the steric factors are eliminated from the reactants, as in acetal **23** discussed above, the more highly substituted enamine (**24**) is the major product.

The magnitude of the preference for the formation of the less substituted enamine from unsymmetrical ketones as expressed by the general rule given above is not entirely clear. House and Schellenbaum (*48*) have reported that 2-methylcyclohexanone and pyrrolidine produce a product mixture of tetra- and trisubstituted enamines in a ratio of 15:85. The estimate of this ratio was made from NMR data. In contrast Stork and co-workers (*9*) report the formation of 100% trisubstituted enamine as determined by NMR spectroscopy.

The piperidine, pyrrolidine, and morpholine enamines of cyclohexanone substituted in the 3-position by methyl, phenyl, and *t*-butyl have been prepared (*49*). The complexity of the NMR spectra in the ethylenic hydrogen region indicated a mixture of isomeric enamines. Estimation of the per cent of each isomer by examination of the NMR spectra was not possible, nor were the isomeric enamines separable by vapor-phase chromatography.

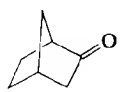
Enamines of several methyl ketones have been prepared and their isomer content estimated by NMR spectroscopy (*13,39,43*). The reaction of $Ti[N(CH_3)_2]_4$ as the amine source and 3-methyl-2-butanone gave only **26** ($R_1 = R_2 = CH_3$), which could be isomerized by prolonged heating to a 1:1 mixture of that enamine and enamine **27** ($R_1 = R_2 = CH_3$) (*39*). The reaction of morpholine and 3-methyl-2-butanone in benzene with a trace of acetic

$CH_2{=}C(NR_1R_2)CH(CH_3)_2$ (26) $\qquad$ $CH_3C(NR_1R_2){=}C(CH_3)_2$ (27)

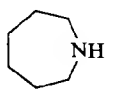
acid or *p*-toluenesulfonic acid gave a 35:65 ratio of **26** to **27** ($R_1{-}R_2 = -CH_2CH_2OCH_2CH_2-$) (*13*). A modified preparation (*43*) of the morpholine enamine of 3-methyl-2-butanone involving titanium tetrachloride, the ketone, and the free amine did produce a mixture of the two enamines (29% **26** and 71% **27**, $R_1{-}R_2 = -CH_2CH_2OCH_2CH_2-$). The modified procedure utilizing dimethylamine gave only **26** ($R_1 = R_2 = CH_3$).

C. Secondary Reactions in Enamine Formation from Ketones and Amines

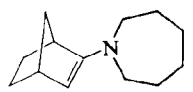
Norcamphor (**28**) and hexamethylenimine (**29**) in xylene containing a catalytic amount of *p*-toluenesulfonic acid gave not only the enamine (**30**) but also the saturated amine (**31**) (*50*). Hexamethylenimine was believed



(28)



(29)



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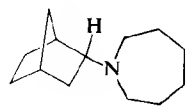
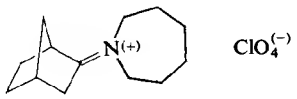


(31)

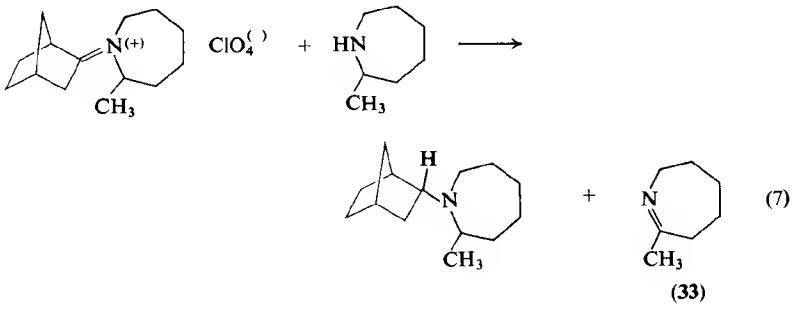
to be the reducing agent since the iminium perchlorate (**32**) could be converted to **31** in 60% yield with an excess of hexamethylenimine. This conclusion was challenged by Patmore and Chafetz (*51*), who found that by



(**32**)

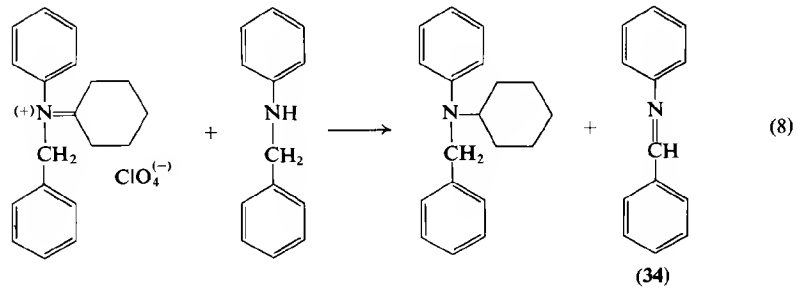
heating at 175–180° the morpholine enamine of cyclohexanone in the presence of *p*-toluenesulfonic acid for 24 hr, N-cyclohexylmorpholine was produced in 23% yield. These authors proposed that the saturated amine is formed from the enamine by an initial protonation to give the iminium salt followed by an intermolecular hydride transfer from a second molecule of enamine.

The reduction was studied in more detail by Cook and Schulz (*52*). They demonstrated conclusively that reduction of iminium salts by secondary amines is possible as illustrated in Eqs. (7) and (8). The oxidation



(**33**)

(7)

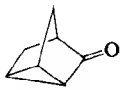


(**34**)

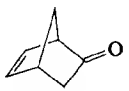
(8)

products, imines (**33** and **34**), were isolated and characterized. These experimental results support the mechanistic pathway involving the secondary amine as the reducing agent. The mechanism proposed by Patmore and Chafetz (*51*) limits the yield of saturated amine to a maximum of 50%, but Cook and Schulz (*52*) observed yields of 50 to 62% for the reduction of four iminium salts. According to Patmore and Chafetz's mechanism, the removal of hydride ion would have to come from a bridgehead position in the case of the bicyclic enamines. This is not energetically favorable. It is conceivable that under the conditions employed by Patmore and Chafetz, which are quite similar to those used by Cook and Schulz, water, present as a contaminant in the enamine or produced by acid-catalyzed condensation reactions of cyclohexanone (a reaction product found by Patmore and Chafetz), caused the hydrolysis of the enamine, and the secondary amine so produced acted as the reducing agent.

The reaction of morpholine with tricyclo[2.2.1.$0^{2,6}$]heptan-3-one (**35**) and with 5-bicyclo[2.2.1]hepten-2-one (**36**) does not proceed in the

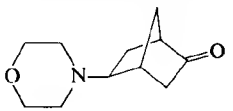


(**35**)

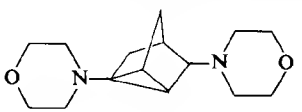


(**36**)

normal manner (*50,53*). The former reaction gave the ring-opened product (**37**) in 64% yield (*50*). The reaction of the unsaturated ketone (**36**) with

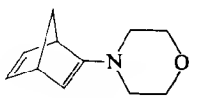


(**37**)



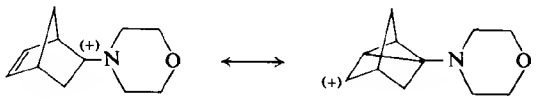
(**38**)

morpholine in the presence of *p*-toluenesulfonic acid gave the diamine (**38**) as the only product in 23% yield (*50*). In neutral media three products were formed: the diamine (**38**) (4%), the enamine (**39**) (2%), and the aminoketone (**37**) (1%). Mechanisms were offered for the formation of the two



(**39**)

unusual products. The mechanism of interest is the one leading to the diamine (**38**). The usual steps in enamine formation as given earlier can produce the carbonium ion (**40**). Attack by another molecule of morpholine would then give the observed product after loss of a proton. Such secondary



(**40**)

reactions suggest that the study of the reaction of secondary amines with other unusual ketones would be intriguing from both mechanistic and synthetic viewpoints.

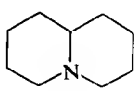
The acid-catalyzed reaction of acetophenone with acyclic secondary amines results in the formation of the expected enamine and a rearrangement product. The latter product arises from the transfer of one of the amino N-alkyl groups to the enamine's β carbon to produce a ketimine (*53a*).

III. Enamines via Mercuric Acetate Oxidation of Tertiary Amines

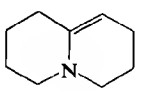
A. General Aspects

The oxidation of amines by mercuric acetate is an old reaction (*54*) which up until recent years was employed primarily to modify alkaloid structures (*55*). A systemic study of the oxidizing action of mercuric acetate by Leonard and co-workers led to the development of a general method for the synthesis of enamines from cyclic tertiary amines. An observation made after a large number of compounds were oxidized, but which is worth noting at the onset, is that a tertiary hydrogen alpha to the nitrogen atom is removed preferentially to a secondary α-hydrogen.

The first compound studied (*56*) was quinolizidine (**41**), which can be readily converted to $\Delta^{1(10)}$-dehydroquinolizidine (**42**) in 60% yield by the action of 4 moles of mercuric acetate in 5% aqueous acetic acid on 1 mole of the amine. Mercurous acetate precipitates as the reaction progresses at



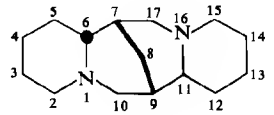
(**41**)



(**42**)

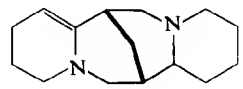
steam-bath temperatures. Extension of the reaction to more complicated systems gave similar results.

Sparteine (**43**) is oxidized to a mixture of isomers: $\Delta^{5,11}$-didehydrosparteine (**44**) and Δ^{5}-dehydrosparteine (**45**) (*57*). The other two stereoisomers of sparteine, α-isosparteine (**46**) (*58,59*) and β-isosparteine (sparteine) (**47**) (*58,60*) have been subjected to mercuric acetate oxidation, each giving $\Delta^{5,11}$-didehydrosparteine (**44**).



(**43**)

(**44**)

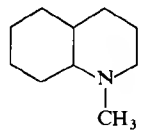


(**45**)

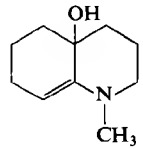
(**46**)

(**47**)

Bicyclic amines with nitrogen at the bridgehead and alpha to the bridgehead have been studied extensively. The methylquinolizidines gave the expected enamines (*61*), while either *cis*- or *trans*-1-methyldecahydroquinoline (**48**) gave a dehydrogenation–hydroxylation product (**49**) (*62*). If the angular position is substituted, as in **50**, oxidation takes place to give (**51**) (*63*).

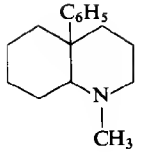


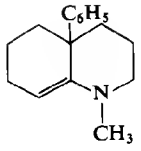
(**48**)



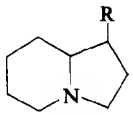
(**49**)

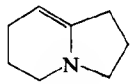
The unsubstituted bicyclic amines, 1-azabicyclo[4.3.0]nonane (**52**, R = H),


(50)

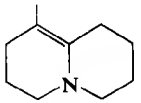

(51)

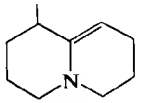
1-azabicyclo[5.3.0]decane, 1-azabicyclo[5.4.0]hendecane, and 1-azabicyclo-[5.5.0]dodecane, have been converted to the corresponding enamine or isomeric enamines (*64*). In a later study (*65*), 1-azabicyclo[4.3.0]nonane (**52**, R = H), several substituted 1-azabicyclo[4.3.0]nonanes, quinolizidine, and 1-methylquinolizidine were dehydrogenated to the corresponding enamine or isomeric enamines. The presence of an isomeric pair and the relative amounts of each were ascertained using NMR spectroscopy. This technique revealed that the mercuric acetate oxidation of **52** (R = H) produces almost exclusively enamine **53** (*65*) rather than the mixture of isomeric enamines as previously believed (*64*). Reinecke and Kray (*65*) proposed several

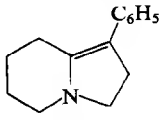

(52)


(53)

generalizations as a result of their study: The double bond of indolizidine enamines (e.g., **53**) prefers to be endo to the six- and exo to the five-membered ring; substituents stabilize the double bond (ratio of **54** to **55** is 2:1); and isomers whose double bonds are conjugated are favored [enamine **56** is the apparent sole product when **52** (R = C_6H_5) is dehydrogenated].

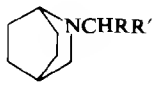

(54)


(55)


(56)

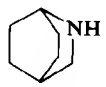
1,4-Diazobicyclo[2.2.2]octane (**57**) is recovered in 80% yield when mercuric acetate oxidation is attempted at room temperature (*66*). However, N-substituted derivatives of 2-azabicyclo[2.2.2]octane (**58**) undergo oxidation readily to give immonium salts (**59**), dealkylation to 2-azabicyclo[2.2.2]-octane (**60**), or lactams (**61**), depending upon the substituent group and the

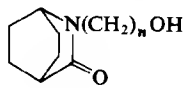

(57)


(58)

reaction temperature (*67*). 2-Methyl- and 2-benzyl-2-azabicyclo[2.2.2]-octane (**58**, R = R′ = H and R = H, R′ = C_6H_5) yield the corresponding


(59)


(60)

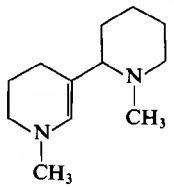

(61)

iminium salts (**59**), while 2-ethyl- and 2-isopropyl-2-azabicyclo[2.2.2]octane (**58**, R = H, R′ = CH_3 and R = R′ = CH_3) are dealkylated to **60**. The amino alcohols (**58**, R = H, R′ = CH_2OH and R = H, R′ = CH_2CH_2OH) when heated at 97° gave 13.5% **61** ($n - 2$) and 45% **61** ($n = 3$), respectively. Such overoxidation has also been noted in pyrrolidino and piperidino amino alcohols (*66,68*). The iminium salts (**59**) cannot be converted to enamines upon treatment with hydroxide since Bredt's rule would be violated. The 3-alkyl-3-azabicyclo[3.3.1]nonanes can also be dehydrogenated to the iminium salts, but once again enamine formation is impossible (*69,70*).


(62)

To return to a more historical development the mercuric acetate oxidation of substituted piperidines (*71*) should be discussed next. This study established that the normal order of hydrogen removal from the αN-carbon is tertiary —C—H > secondary —C—H > primary —C—H, an observation mentioned earlier in this section. The effect of substitution variations in the piperidine series can be summarized as follows: 1-methyl-2,6-dialkyl and 1-methyl-2,2,6-trialkyl piperidines, as model systems, are oxidized to the corresponding enamines; the 1,2-dialkyl and 1-methyl-2,5-dialkyl piperidines are oxidized preferentially at the tertiary α-carbon; the 1-methyl-2,3-dialkyl piperidines gave not only the enamines formed by oxidation at the tertiary α-carbon but also hydroxylated enamines as found for 1-methyldecahydroquinoline (**48**) (*62*); 1-methyl-2,2,6,6-tetraalkyl piperidines and piperidine are resistant to oxidation by aqueous mercuric acetate; and

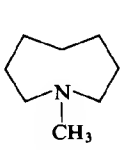
1-methylpiperidine gave 1,1′-dimethyl-Δ^2-tetrahydroanabasine (**63**) in 67% yield presumably by the dimerization of the expected initial oxidation product. Both the enamine and the Δ^2-tetrahydroanabasine were formed when 1,4,4-trimethylpiperidine was oxidized. Similar results were also



(63)

noted when a series of methyl-substituted pyrrolidines were subjected to mercuric acetate oxidation (*72*).

Extension of these studies to medium rings produced interesting results (*73*). The mercuric acetate oxidation of 1-methyl-1-azacyclooctane (**64**), when worked up in the usual manner, gave no distillable material. When an equivalent amount of hydrochloric acid was added to the solution which had been saturated with hydrogen sulfide to precipitate the excess mercuric acetate and filtered, evaporation of the solution to dryness gave a solid which was subsequently identified as 2,4,6-tris(6′-methylaminohexyl)-trithiane trihydrochloride (**65**). Two plausible routes to the observed



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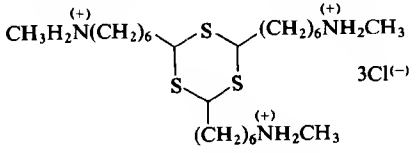
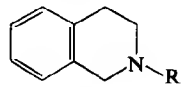


(65)

product were postulated. Hydrolytic cleavage of the enamine would give 7-methylaminoheptanal, which would be converted to the aminothioaldehyde by the excess hydrogen sulfide. Trimerization of the aminothioaldehyde in the acidic medium would give the trithiane trihydrochloride (**65**). The aminothioaldehyde could also be obtained by direct cleavage of the enamine with hydrogen sulfide.

Knabe has introduced mercuric acetate plus ethylenediaminetetraacetic acid (EDTA) as an oxidizing agent for tertiary amines (*74*). The solvent employed is 1% aqueous acetic acid. In this system, the complexed mercuric ion is reduced to elemental mercury. Knabe's studies have centered on the

oxidation of synthetic and naturally occurring 2-alkyl-1,2,3,4-tetrahydroisoquinolines (**66**) (*75*) which bear various substituents in the 1, 2, 3, and 4 positions. The primary products (dependent upon the substitutent groups)



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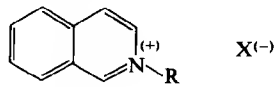
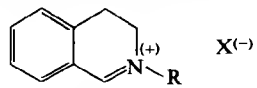
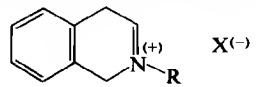


(67)

are the 2-alkylisoquinolinium salts (**67**) and the 2-alkyl-3,4-dihydro- and 2-alkyl-1,4-dihydroisoquinolinium salts (**68** and **69**, respectively). Mercuric



(68)

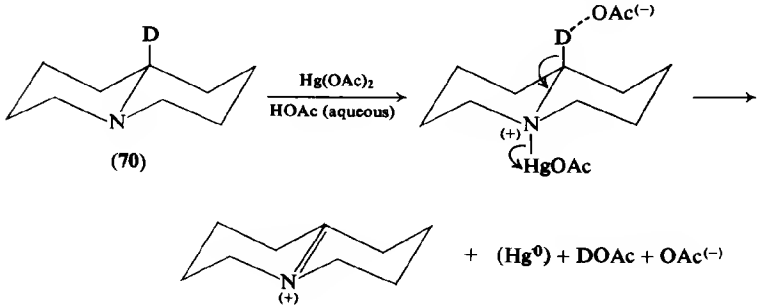


(69)

ion complexed with EDTA will oxidize sparteine (**43**) to Δ^5-dehydrosparteine (**45**) (*74*).

B. Mechanistic Considerations

The mechanism proposed (*56*) for the mercuric acetate oxidation of tertiary amines involves the initial formation of a mercurated complex through the electron pair on nitrogen followed by a concerted removal of a proton from an α carbon and cleavage of the mercury–nitrogen bond [Eq. (9)]. This four-center elimination implies that the removal of the α hydrogen is the rate-determining step and also that a *trans*-coplanar relationship exists between the proton being removed and the nitrogen–mercury complex. To determine if the breaking of an α carbon–hydrogen bond is the rate-determining step, the oxidation of quinolizidine-10-*d* (**70**)



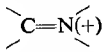
(70)

+ (Hg^0) + DOAc + $OAc^{(-)}$ (9)

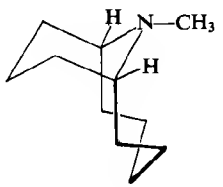
was carried out (*76*). Quinolizidine was found to react faster than quinolizidine-10-*d* by a factor of about 2.3. This factor was arrived at by spectral determination of the amount of enamine and by weighing the mercurous acetate precipitated after a given time interval. Importantly, the quinolizidine-10-*d* recovered after partial oxidation was of unchanged deuterium content.

These experiments verified that cleavage of the C—H bond is occurring in the rate-limiting step, but proof of the necessity of a *trans* relationship of the C—H to the nitrogen–mercury complex was lacking. Indications that such a relation was necessary are found in studies of the mercuric acetate oxidation of alkaloids, which will be discussed subsequently.

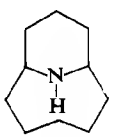
The bicyclic amine 11-methyl-11-azabicyclo[5.3.1]hendecane (**71**) provided a model system in which the hydrogens on the equivalent α-tertiary-carbon atoms cannot be *trans* to the nitrogen–mercury bond in the mercurated complex and in which epimerization at these α carbons is impossible (*77*). This bicyclic system is large enough to accommodate a



bond at the bridgehead. When the amine (**71**) was oxidized, demethylation to the secondary amine (**72**) occurred since one of the hydrogens of the N-methyl group, which has essentially unrestricted rotation, not the hydrogens at C-1 and C-7, could be aligned *trans* coplanar with the nitrogen–mercury complex. The lack of any hydrogens which could be aligned *trans* coplanar with the nitrogen–mercury complex explains the previously mentioned failure of 1,4-diazabicyclo[2.2.2]octane (**57**) to undergo mercuric acetate oxidation (*66*).



(**71**)



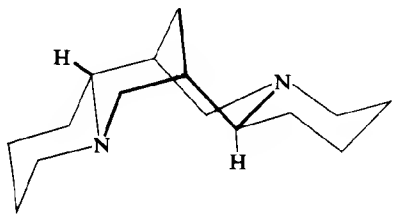
(**72**)

The mechanistic sequence as outlined for quinolizidine-10-*d* has metallic mercury as the reduced species. Mercurous acetate is the form in which the mercury eventually appears. It has been shown (*76*) that under the standard operating conditions, mercuric acetate will oxidize metallic mercury to the

mercurous form. The proposal that a two-electron transfer occurs appears reasonable (*56*). As noted previously, when mercuric ion complexed with EDTA is used, metallic mercury is formed (*74*). Redox studies (*78*) of both oxidation systems have revealed the formation of mercurous ion as a common reaction intermediate.

The results observed in the oxidation of alkaloids which indicated something of the stereochemistry required for oxidation and prompted studies on model systems can now be interpreted more confidently. However, care must be used when basing steric differentiation on mercuric acetate oxidation studies since conditions must be employed which avoid epimerization at carbons alpha to the nitrogen.

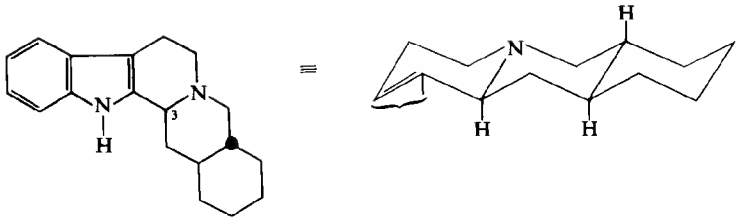
The oxidation of sparteine (**43**) can give either dehydro- (**45**) or didehydrosparteine (**44**). The hydrogen at C-6 is lost readily at room temperature to give dehydrosparteine (*57*), while refluxing is necessary to form didehydrosparteine (*79*). Thus the hydrogen which is axial to two rings and to the electron pair on nitrogen is the one lost first. In analyzing these data it was assumed that all rings are in the chair form (*77*). On the basis of a variety of observations the preferred conformation of sparteine is now believed to be **73** with ring C in the boat form (*80*).



(**73**)

In β-isosparteine (**47**) both tertiary protons at C-6 and C-11 are arranged in the *cis* position to the free electron pair on nitrogen as indicated by the NMR spectrum (*80*). Much earlier X-ray analysis showed that all rings in crystalline α-isosparteine (**46**) are present in stable chair conformations (*81*). A comparative rate (extrapolated) at 65° for α-isosparteine (5.0) and sparteine (1.0) has been calculated (*82*). Also it has been reported that β-isosparteine gave the dehydro derivative under mild conditions and the didehydro under more drastic conditions (times, temperatures not given) (*60*).

The indole alkaloids of the yohimbine–reserpine series exist in four configurations: normal (**74**), allo (**75**), pseudo (**76**), and epiallo (**77**). The results of the mercuric acetate oxidation of the indole alkaloids are in general



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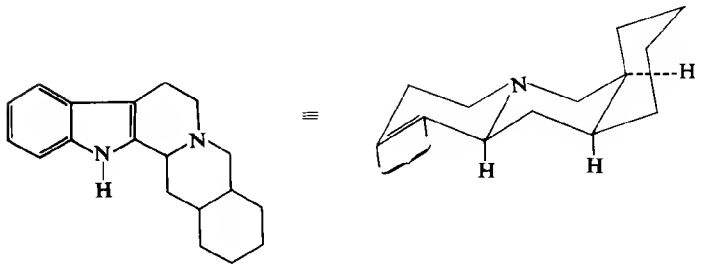

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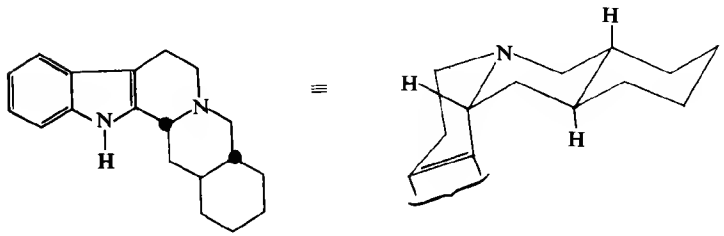

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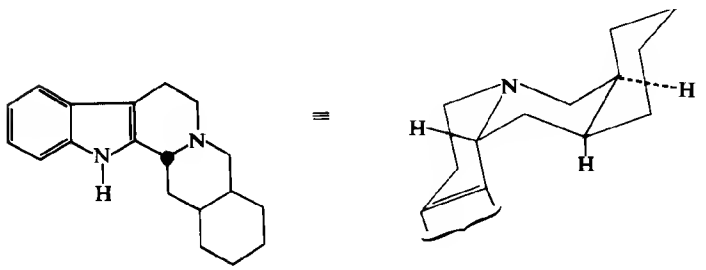
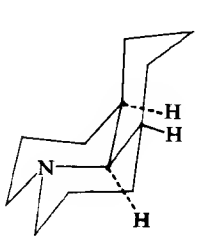


(77)

accord with the proposed *trans*-coplanar mechanism: namely, compounds with the normal (e.g., yohimbine) (*83*) and allo (allo- or α-yohimbine, isoreserpine) (*84*) are more readily oxidized at C-3 by mercuric acetate than those with the pseudo (pseudoyohimbine) (*83*) and epiallo (epialloyohimbine, reserpine) (*84*) configurations.

Bohlmann and Arndt (*85*) have separated the possible stereoisomers of hexahydrojulolidine (**78–80**) and subjected them to mercuric acetate oxidation. The rates, which were followed by the precipitation of mercurous acetate, showed that isomer **78** reacted about five times faster than isomer **79**, while isomer **80** reacted very slowly. The difference in rates between **78** and **79**, both of which have tertiary α-hydrogens *trans* to the nitrogen electron pair, was explained by pointing out that greater relief of nonclassical strain occurs in the oxidation of **78** as compared to **79**. Isomer **80** has no tertiary α-hydrogens *trans* to the nitrogen electron pair except when it is in an unfavorable boat conformation.



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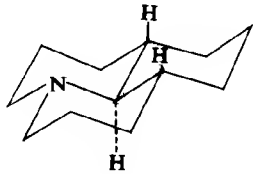

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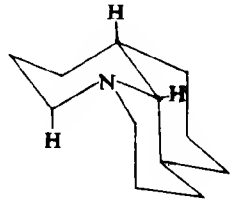
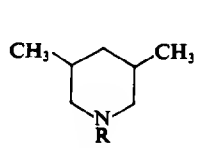


(80)

A kinetic study of the mercuric acetate oxidation of 1-alkyl-3,5-dimethylpiperidines (**81**) and 3-alkyl-3-azabicyclo[3.3.1]nonanes (**82**) was made to evaluate the effect of the N-alkyl group on the rate of oxidation and to contrast these two ring systems (*70*). The maximum factor in the piperidine



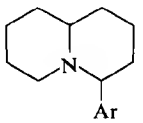
(81)

(82)

system was 2.15 (1.00 for **81**, R = *t*-butyl, and 2.15 for **81**, *R* = *n*-propyl) and in the bicyclic system 6.00 (1.00 for **82**, R = methyl, and 6.00 for **82**, R = *n*-butyl). Thus the size of the alkyl group had little or no effect in the

piperidine series and a moderate effect in the bicyclic series, but not in an order based on the usual steric effects of the groups. The order within a series did not depend on the relative basicities of the amines. The oxidation followed reasonable second-order kinetics. As illustrated by the rate constants for 1,3,5-trimethylpiperidine (1.92×10^{-4}, 70°) and 3-methyl-3-azabicyclo[3.3.1]nonane (0.64×10^{-3}, 50°), the bicyclic amines reacted many times more rapidly than the monocyclic amines. A possible explanation, similar to that offered to rationalize differences in rates between the hexahydrojulolidine isomers **78** and **79** (*85*), is the greater relief of non-bonded interactions in the amine–mercuric acetate complexes of the bicyclic amines when product is formed.

Conformational effects appear to be important in determining which tertiary α-hydrogen is removed. For example, 4-phenyl-, 4-*p*-nitrophenyl-, and 4-*p*-methoxyphenylquinolizidine (**83**) all are oxidized to the corresponding $\Delta^{5(10)}$-iminium salts (**84**) and not to the conjugated Δ^{4}-iminium salts (**85**) (*86*). The authors judged that steric hindrance was responsible or that the conformation of the 4-substituted quinolizidines did not contain ideal



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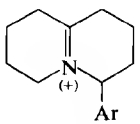

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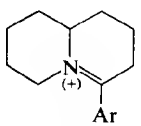
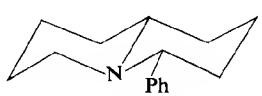


(85)

chairs, so that the *trans* hydrogen on C-4 was not coplanar with the unshared pair of electrons on the nitrogen atom. Even 4-methylquinolizidine is oxidized to the $\Delta^{5(10)}$-iminium salt (*61*). In both of these studies it was not stated whether a pure epimer or a mixture of epimers was oxidized. A later report (*80*) did give the NMR spectra of both epimers of 4-phenylquinolizidine (**86**, *trans*; **87**, *cis*). The *trans* epimer was shown to yield the $\Delta^{5(10)}$-iminium salt (**84**, Ar = C_6H_5).



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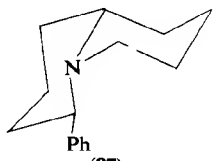
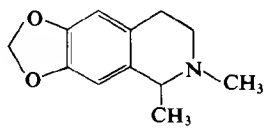


(87)

The substituted 1,2,3,4-tetrahydroisoquinolines studied by Knabe and Roloff (*87*) also produce some puzzling results difficult to rationalize when oxidized with mercuric EDTA. Compounds **88** and **89** are not attacked to

any great extent while several higher alkyl derivatives (**90**, R = ethyl, *t*-butyl, *n*-butyl; R′, R″ = —OCH_3 or —OCH_2O) are oxidized. Oxidative dimerization takes place when 6,7-dimethoxy-1,2-dimethyl-1-ethyl-1,2,3,4-tetrahydroisoquinoline is treated with mercuric EDTA (*87a*).

It was found, during a study of synthetic routes leading to quinine analogues, that oxidation of a specific bicyclic pyrazoline derivative with mercuric acetate gives an enamine-like pyrazole (*87b*).



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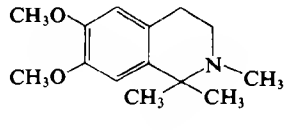

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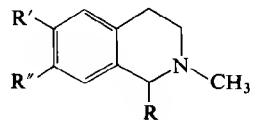
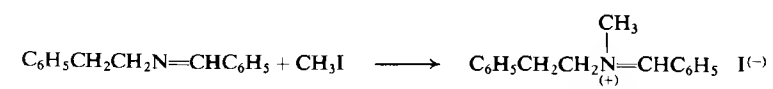


(90)

IV. Synthesis of Iminium Salts

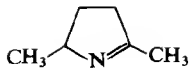
The preceding section described the preparation of enamines by mercuric acetate oxidation of tertiary amines. The initial product in these oxidations is the ternary iminium salt, which is converted to the enamine or mixture of enamines by reaction with base. Thus iminium salts synthesized by methods other than the oxidation of tertiary amines or the protonation of enamines are potential enamine sources.

The alkylation of imines by an alkyl halide to give an iminium salt will be illustrated by selected reactions over a period of years. A more complete survey is available (*88*). Decker and Becker (*89*) prepared a number of iminium salts (**91**, for example) by mixing methyl iodide and aromatic imines in benzene. 2,5-Dimethyl-2-pyrroline (**92**) has been alkylated and the



(91)

product (**93**) decomposed by potassium hydroxide to yield 1,2,5-trimethyl-Δ^{2}-pyrroline (**94**) (*90*). It is probable that the endocyclic enamine (**94**) was



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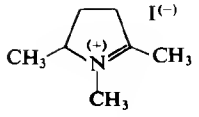

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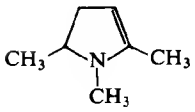

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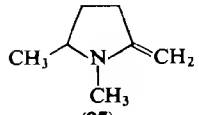
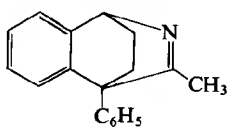


(95)

contaminated with the exocyclic enamine (**95**) since 1,2-dimethyl-Δ^2-pyrroline has been shown to be in equilibrium with its exocyclic isomer (*91*). The bicyclic exocyclic enamine (**98**) has been prepared by alkylation of the imine (**96**) followed by treatment of the iminium salt (**97**) with base (*92*). This route gave a purer product in better yield than the mercuric acetat oxidation of the tertiary amine (**99**).



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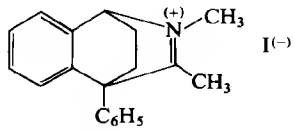

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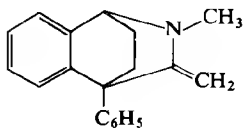

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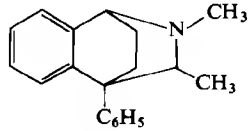
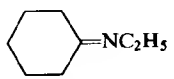


(99)

A variation on the alkylation of imines which yields enamines directly has been developed (*93*). The imine is converted to the ambident ion by sodium amide or sodium hydride. An alkylating agent [$(CH_3CH_2)_3OBF_4$, $(CH_3CH_2)_2SO_4$ or CH_3CH_2I] is then added to the cooled solution of the imine anion. For example, N-ethylcyclohexanone imine (**100**) can be converted to 1-diethylaminocyclohexene (**101**) in 53% yield using sodium amide as the base and $(CH_3CH_2)_3OBF_4$ as the alkylating agent.



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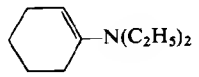
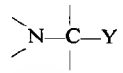
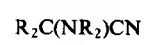


(101)

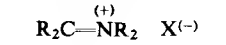
Ternary iminium salts have been prepared by cleavage of a covalent C—Y bond in a



system (*88*). Either silver nitrate or silver iodide can be added to a solution of appropriately substituted aliphatic amino nitriles (**102**) in absolute ethanol to give the corresponding iminium salts (**103**) in yields ranging from 20 to 60% (*94*). In a similar vein, trityl salts oxidize tertiary amines by means of a hydride transfer mechanism to produce iminium salts (*94a*).

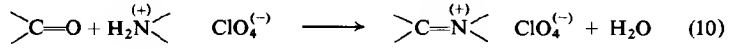


(102)



(103)

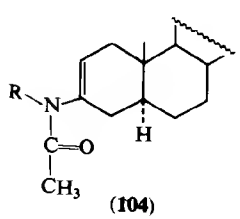
Ternary iminium complex salts can be prepared by direct combination of an aldehyde or ketone with a secondary amine complex salt (*95*). An adaptation of this procedure employing the perchlorate salts of secondary amines provides a simple method for the preparation of the readily crystallized and nonhydroscopic ternary iminium perchlorates (*96*), Eq. (10).



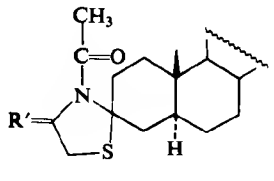
(10)

V. Enamines by Reductive Processes

The preparation of enamines by reduction of aromatic heterocyclic bases and their quaternary salts or of lactams is not the most useful approach (*97*). The lithium aluminum hydride reduction of N-acyl enamines has been used with both fruitful and unsuccessful results. A series of 3-N-acetyl-Δ^2-cholestenes (**104**) has been prepared by desulfurization of the appropriate thiazolidine (**105**) (*98,99*). Lithium aluminum hydride reduction of the



(104)



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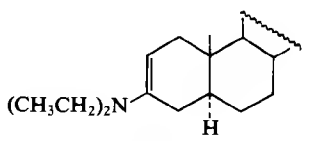
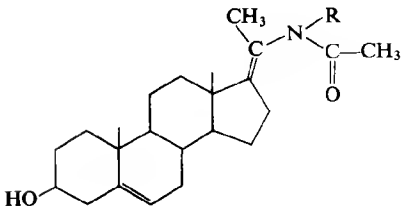
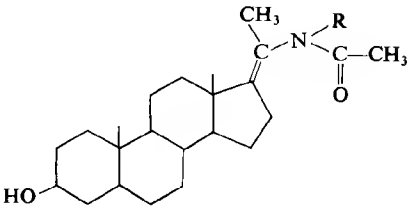


(106)

N-acyl enaminc (**104**, R = CH_3CH_2) gave an unstable enamine (**106**) which decomposed readily to 3-cholestanone. The steroidal N-acetyl enamines (**107** and **108**, R = $C_6H_5CH_2$) can be reduced by lithium aluminum hydride in tetrahydrofuran to the corresponding enamines (**109**, R = $C_6H_5CH_2$) in 90 and 68% yield, respectively (*100*). Attempts to reduce the enamide (**107**, R = CH_3) led to the formation of the impure enamine (**109**, R = CH_3), which decomposed to the hydroxy ketone (**110**).



(107)



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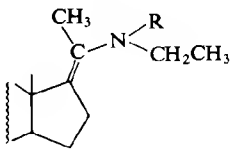
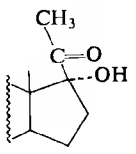
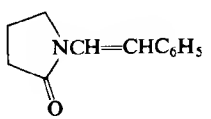


(109)

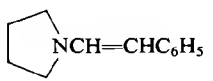


(110)

The simpler enamide, 1-styryl-2-pyrrolidone (**111**), is reduced by lithium aluminum hydride in refluxing ether to 1-styrylpyrrolidine (**112**) in 52% yield (*101*).

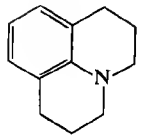


(111)

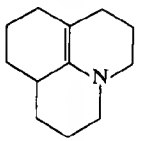


(112)

The lithium-*n*-propylamine reducing system has been found capable of reducing julolidine (**113**) to Δ^5-tetrahydrojulolidine (**114**, 66% yield) and 1-methyl-1,2,3,4-tetrahydroquinoline to a mixture of enamines (87% yield), 1-methyl-Δ^8-octahydroquinoline (**115**) and 1-methyl-Δ^9-octahydroquinoline (**116**) (*102*). This route to enamines of bicyclic and tricyclic systems avoids hydroxylation, which occurs during mercuric acetate oxidation of certain bicyclic and tricyclic tertiary amines (*62,85*; see Section III.A).



(113)



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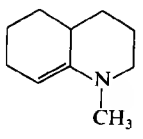

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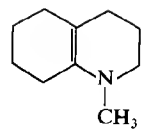
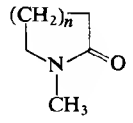


(116)

VI. Enamines from Lactams and Grignard Reagents

This method of preparation has been devcloped primarily by Lukeš (*103,104*). N-Methyl lactams (**117**) with five- and six-membered rings plus Grignard reagents yield the 1-methyl-2-alkyl pyrrolines (**118**, $n = 1$) and 1-methyl-2-alkylpiperideines (**118**, $n = 2$), respcctively, plus 2,2-dialkylated bases (**119**) as by-products (*103*). For example, 1,3-dimethyl-2-piperidone



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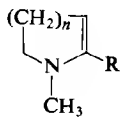
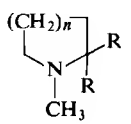
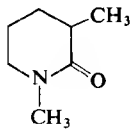


(118)



(119)

(**120**) with a threefold excess of ethylmagnesium iodide yielded 40% of 2,2-diethyl-1,3-dimethylpiperidine (**121**) and 32% of 1,3-dimethyl-2-ethyl-Δ^2-tetrahydropyridine (**122**) (*71*). If the position alpha to the lactam carbonyl



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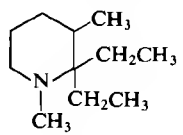

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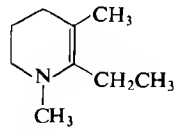
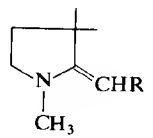


(122)

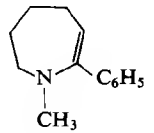
is disubstituted, exocyclic enamines (**123**, R = H or CH_3) are produced (*105*).



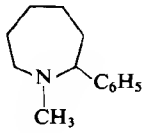
(123)

This method provides a route to certain medium-ring sized enamines (*106,107*) not obtainable by other methods. 1-Methyl-2-phenyl-1-azacyclohept-2-ene (**124**) can be prepared by the reaction of N-methylcaprolactam

with phenyl magnesium bromide (*106*). Mercuric acetate oxidation of 1-methyl-2-phenyl-1-azacycloheptane (**125**), however, gave the open-chain amino ketone (**126**) (*106*).



(**124**)



(**125**)

$CH_3NH(CH_2)_5COC_6H_5$

(**126**)

VII. Synthesis of Enamines Utilizing Various Compounds of Phosphorus, Titanium, Boron, Arsenic, and Mercury

During the past seven years and particularly during 1966 and 1967 several syntheses of enamines utilizing compounds of the elements given in the title of this section have been developed.

Speziale and his co-workers have carried out comprehensive studies of the reactions of phosphorus compounds. It has been shown (*108*) that the reaction of N,N-dialkyl-α-trichloroacetamides (**127**) with phosphites and phosphines gives trichlorovinylamines (**128**). In general the trialkylphosphines gave somewhat higher yields (60 to 83%) and purer products

$$\underset{\textbf{(127)}}{Cl_3CCO(NR_2)} + R'_3P \rightarrow \underset{\textbf{(128)}}{Cl_2C{=}CCl(NR_2)} + R'_3PO$$

than the phosphorous esters. An additional advantage in using the trialkylphosphines is that the reaction can be carried out at room temperature rather than at 150°, as is necessary with the phosphorous esters.

In a later paper Speziale and Smith (*109*) investigated the reaction of trivalent phosphorus compounds with N-monosubstituted α-trichloroacetamides and α-trichloroacetamide. The products were imidoyl chlorides (**129**) and dichloroacetonitrile (**130**), respectively. The intermediacy of enamines (**131**) was assumed. For the monosubstituted amides the enamine

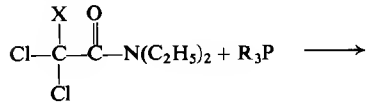
$$\underset{\textbf{(129)}}{Cl_2CHC(=NR)Cl} \qquad \underset{\textbf{(130)}}{Cl_2CHCN}$$

(**131**, $R = C_6H_5$ or C_2H_5) can tautomerize to the more stable imidoyl

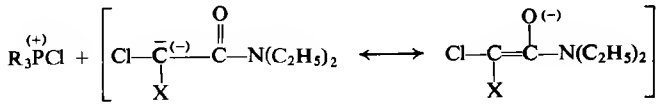
$$\underset{\textbf{(131)}}{Cl_2C{=}CCl(NHR)}$$

chloride (**129**). The unsubstituted amide would give an enamine (**131**, R = H) which could also tautomerize to an imidoyl chloride (**129**, R = H) which in turn would yield dichloroacetonitrile.

In this paper Speziale and Smith (*109*) described experiments which led them to modify the mechanism proposed earlier (*108*) for the reaction of trivalent phosphorus compounds with haloamides. The first step is considered to be attack of the trivalent phosphorus compound on a chlorine atom of the halo amide (**132**) to produce a resonance-stabilized enolate ion (**133**). This is reasonable since under conditions where the trichloroamide

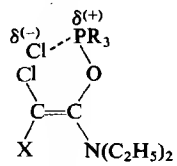


(**132**)



(**133**)

(**132**, X = Cl) and N,N-diethyl-2,2-dichlorophenylacetamide (**132**, X = C_6H_5) react readily and in high yield, the fluoroamide (**132**, X = F), the dichloropropionamide (**132**, X = CH_3), and the dichloroacetamide (**132**, X = H) react poorly. These results support the contention that in the first step a negative charge is formed which is stabilized by the ability of a chlorine atom (**133**, X = Cl) and a phenyl group (**133**, X = C_6H_5) to delocalize electrons through resonance. The next step involves the formation of an intermediate ion pair (**134**). That the chloride ion is ion-paired is indicated



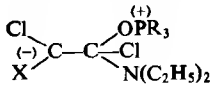
(**134**)

by the fact that no N,N-diethyl-1-bromo-2,2-dichlorovinyl amine (**135**) can be detected by vapor-phase chromatography when the reaction of N,N-diethyl-2,2,2-trichloroacetamide (**132**, X = Cl) and tributylphosphine was carried out in chloroform solution in the presence of a molar equivalent of tetrapropylammonium bromide.

$Cl_2C{=}CBr[N(C_2H_5)_2]$

(135)

Intermediate **134** could then collapse to **136**, which upon loss of the trialkyl- or triarylphosphine oxide would give the enamine (**137**). The conversion of **134** to **137** is probably best viewed as a concerted process.



(136)

$ClXC{=}CCl[N(C_2H_5)_2]$

(137)

It has been reported by Burgada (*109a*) that highly enolized ketones form enamines when they are treated with tris[dimethylamino]phosphine. Only condensation products are formed when slightly enolized ketones are treated with this reagent.

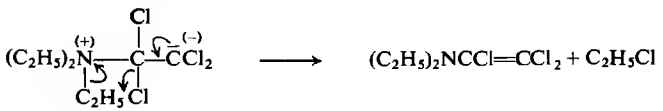
Seyferth et al. (*110*) have also synthesized N,N-diethyl-trichlorovinylamine (**128**, $R = C_2H_5$) from the reaction of triethylamine and phenyl(trichloromethyl)mercury (**138**). The best yield was 23%, obtained when a benzene solution of the amine (45 mM) was added to a refluxing solution of phenyl(trichloromethyl)mercury (10 mM) in benzene. Although no mechanistic study was attempted because of the low yields and the intractable nature of the reaction mixture, the authors proposed the following mechanistic sequence:

$$\underset{\textbf{(138)}}{C_6H_5HgCCl_3} + (C_2H_5)_3N \longrightarrow \underset{\textbf{(139)}}{[C_6H_5HgN(C_2H_5)_3]^{(+)}CCl_3^{(-)}}$$

$$\textbf{(139)} \longrightarrow [CCl_2] + C_6H_5HgCl + (C_2H_5)_3N$$

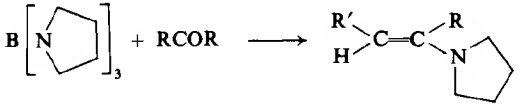
$$(C_2H_5)_3N + [CCl_2] \longrightarrow (C_2H_5)_3\overset{(+)(-)}{N}CCl_2$$

$$(C_2H_5)_3\overset{(+)(-)}{N}CCl_2 + [CCl_2] \longrightarrow (C_2H_5)_3\overset{(+)}{N}CCl_2\overset{(-)}{C}Cl_2$$



All but the last step in the sequence was supported by precedents in th literature or by additional experimentation.

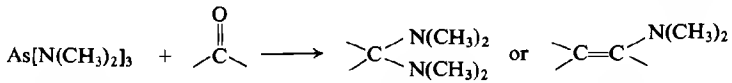
Nelson and Pelter (*44*) have shown that a mixture of tripyrrolidinylborane (**140**) (1.1 mole), a ketone (1 mole), pyrrolidine (1.4 mole), and a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene for about 30 min gave



(140) **(141)**

the corresponding pyrrolidine enamine (**141**) in 70–85% yield. The formation of the enamine is slow if free base is absent, or if there is no acid catalyst. No mechanism for the reaction was proposed, although it is probably similar to that given by Nelson and Pelter (*44*) for the conversion of carboxylic acids to amides using trisdialkylaminoboranes.

Both von Hirsch (*111*) and Weingarten and White (*39*) have reported the amination of aldehydes and ketones by tris(dimethylamino)arsine (**142**) to yield the corresponding gem diamine (**143**) or enamine (**144**). Von Hirsch's

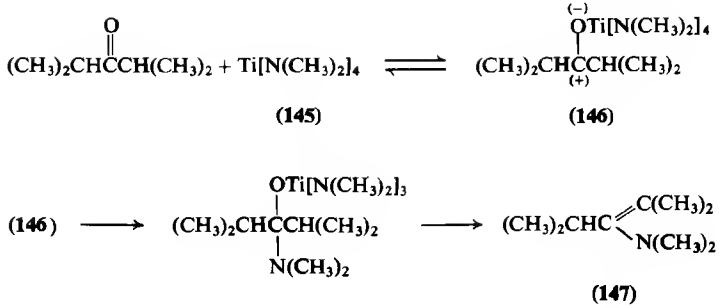


(142) **(143)** **(144)**

yields ranged from 67–87%, while Weingarten and White's yields were about 10% higher (when direct comparisons could be made). Weingarten and White's use of toluene or diethyl ether as a diluent might be the reason. This method is quite useful since it offers a way by which the dimethylamine group can be introduced without using dimethylamine itself. Von Hirsch (*111*) extended the method to the preparation of piperidino- and pyrrolidinoenamines in 80% yield using tripiperidinoarsine and tripyrrolidinoarsine.

A reagent more reactive than tris(dimethylamino)arsine employed by Weingarten and White (*39*) was tetrakis(dimethylamino)titanium (**145**). With this compound it was possible to prepare N,N-dimethyl(1-isopropyl-2-methylpropenyl)amine (**147**) from diisopropyl ketone. Weingarten and White (*39*) have suggested a possible mechanism for this reaction (see p. 88). If benzaldehyde (*39,111*), formaldehyde (*111*), or acetaldehyde (*39*) is used, the corresponding gem diamine or aminal (**143**) is formed.

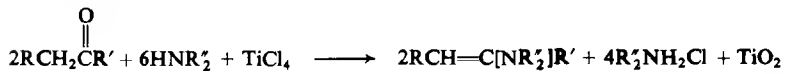
Since tetrakis(dialkylamino)titanium compounds must be synthesized, White and Weingarten (*43*) sought a more versatile synthetic pathway.



(145) (146)

(147)

They found that a stoichiometric mixture of titanium tetrachloride, secondary amine, and aldehyde or ketone produced enamines directly and rapidly [Eq. (11)].



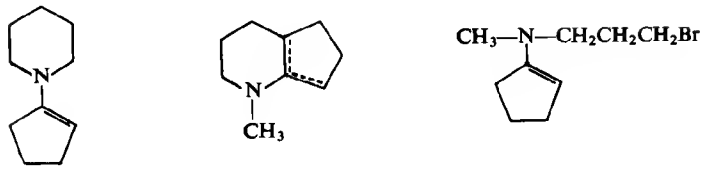
(11)

The yields ranged from 55% for the mixture of enamines formed from morpholine and methylisopropyl ketone to 94% for the enamine formed from dimethylamine and methyl *t*-butyl ketone. The hindered ketone 2,5-dimethylcyclopentanone could be converted to an enamine, but the more hindered ketone, 2,6-di-*t*-butylcyclohexanone, was inert. White and Weingarten (*43*) attribute the effectiveness of titanium tetrachloride in this reaction to its ability to scavenge water and to polarize the carbonyl bond.

VIII. Miscellaneous Preparations

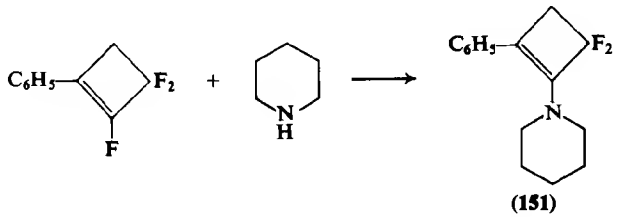
Most of the following methods represent less general preparative routes to enamines. In some examples the enamines produced can be obtained via methods already described in preceding sections, while in other examples the enamines produced are uniquely synthesized. In an attempt to present these miscellaneous preparations in other than a random order, they have been divided into reactions involving alkylations (A) and "others" (B).

A. 1-(1-Cyclopenten-1-yl)piperidine (**148**) reacted with N-methyl-3-bromopropylamine hydrobromide to yield 74% of a mixture of enamines (**149**) (*112*). The proposed mechanism involved an amine exchange to give the enamine **150** which underwent internal alkylation.

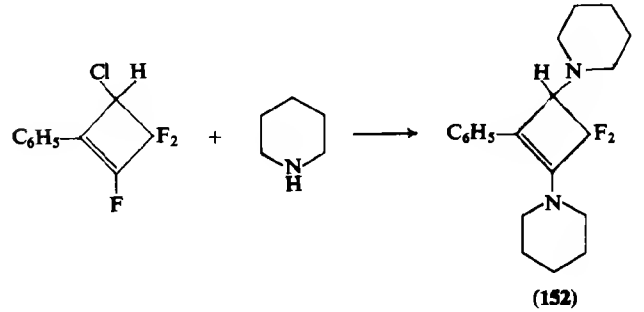


(148) (149) (150)

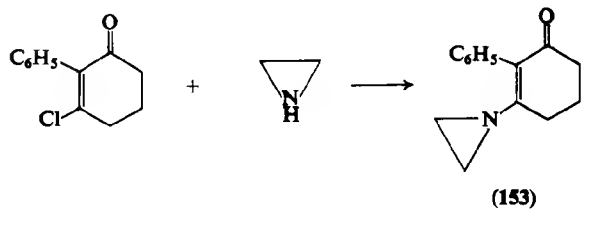
Displacement of vinyl fluorine or chloride by secondary amines has given some unusual enamines as illustrated for the preparation of 1,1-difluoro-2-piperidino-3-phenyl-2-cyclobutene (**151**) (*113*), 1,1-difluoro-2,4-dipiperidino-3-phenyl-2-cyclobutene (**152**) (*114*), and 2-phenyl-3-(1′-aziridinyl)-2-cyclohexenone (**153**) (*115*).



(151)

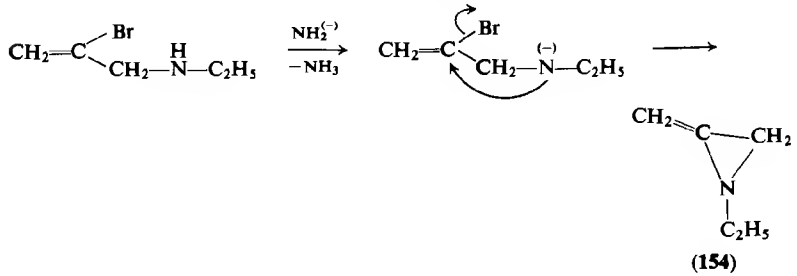


(152)

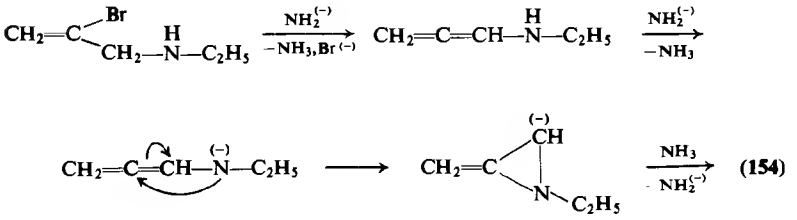


(153)

N-(2-Bromoallyl)-ethylamine with sodium amide in liquid ammonia gave N-ethylallenimine (**154**) by either of the paths shown (*116,117*).



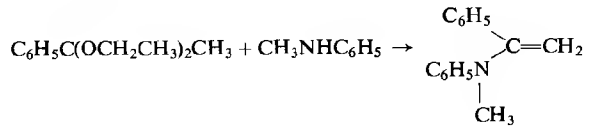
(**154**)



(**154**)

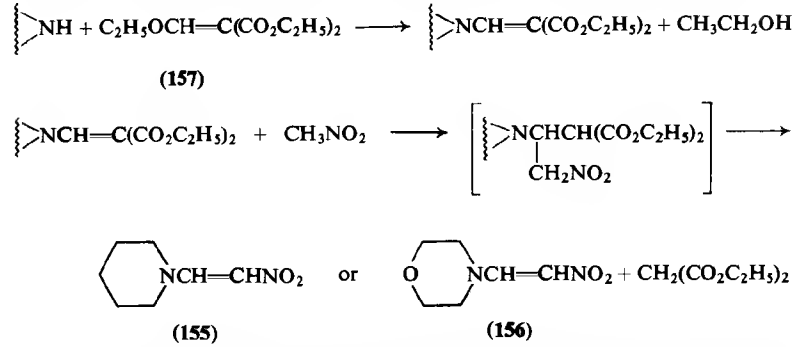
Fulvene-type enamines, which possess some nonbenzenoid aromatic character, have been synthesized by treating cyclopentadienylsodium with an amide–dimethyl sulfate complex (*117a,117b*) or quaternary pyridinium salts (*117c*). One of the simplest ones produced is 6-(dimethylamino)fulvene (*117a,117d*).

B. The preparation of enamines by heating secondary amines and ketals was originated by Hoch (*118*) and has been extended by Bianchetti and co-workers (*119–121*).



1-Piperidino-2-nitroethene (**155**) and 1-morpholino-2-nitroethene (**156**) were the final products when a slight excess of the appropriate secondary amine was caused to react with ethoxymethylenemalonate (**157**) in the

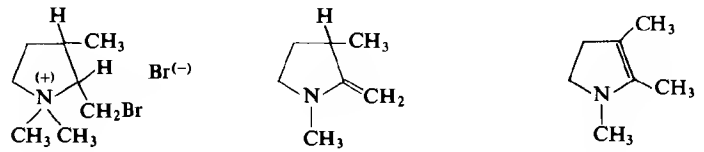
presence of nitromethane (*122*). The reaction sequence proposed was:



(**155**) (**156**)

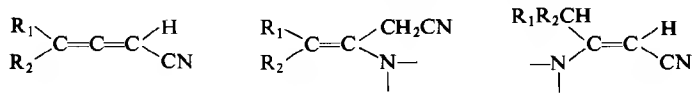
This method was extended to the preparation of aminonitropropenes, but only piperidine and morpholine of the several secondary amines studied were found effective.

The dehydrobromination and dequaternization of 1,1,3-trimethyl-2-bromomethylpyrrolidinium bromide (**158**) has been accomplished by dry distillation from potassium acetate (*123*). Since the product was isolated as the perchlorate salt, no conclusion can be drawn as to whether the original reaction mixture contained the exocyclic enamine (**159**) or the endocyclic enamine (**160**) or a mixture of both.



(**158**) (**159**) (**160**)

The addition of secondary amines to 1-cyanoallenes (**161**) results in the formation of enamines in 80–90% yield (*124*). Addition can occur at the 1,2 or 2,3 double bonds so that a mixture of isomeric enamines (**162** and **163**) is formed. The ratio of products is influenced by the alkyl substituents on the cyanoallenes and the structure of the secondary amine.



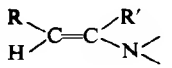
(**161**) (**162**) (**163**)

Van Tamelen (*124a*) has reported a useful and specific synthetic method for the production of enamines by the oxidative decarboxylation of N,N-dialkyl α-amino acids with sodium hypochlorite.

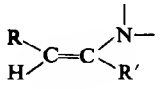
Treatment of allylamines with potassium amide on alumina causes their isomerization to enamines in good yields (*124b*). When allylamines are heated to about 55° the same type of isomerization takes place (*124c*).

IX. Stereospecific Synthesis of Enamines

The reaction of a secondary amine with a ketone or with an open-chain aldehyde gives a mixture of isomers **164** and **165** (R′ = H, alkyl, or aryl). No consistent policy has been established as to which isomer is considered

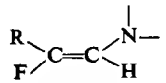


(164)



(165)

to be *cis* and which *trans*. The ratio of the two isomers is determined primarily by thermodynamic control (*125*). Some attempts have been made to investigate the isomer content of reactions which were not designed nor claimed to be stereospecific. The Raman and infrared spectra of a series of enamines prepared from both aldehydes and ketones (*18*) indicated that the *trans* isomer (**164**) predominated, but not to the total exclusion of the *cis* (**165**). The NMR spectra of enamines prepared from α-fluoroaldehydes revealed the presence of *cis* (**166**) and *trans* (**167**) isomers (*27*). No estimation of the relative amounts of each isomer for a particular enamine was given.



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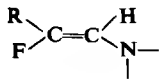
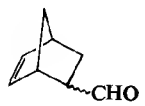


(167)

An example of the use of NMR spectroscopy to ascertain with reasonable certainty the stereochemistry of a series of enamines has been provided by Paquette (*25*). Based on a study of the NMR spectra of the endo- and exo-5-norbornene-2-carboxaldehydes (**168**), the enamine mixtures were estimated to contain 80 to 90% of the transoid form (**170**).



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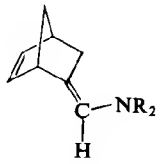

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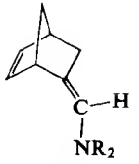
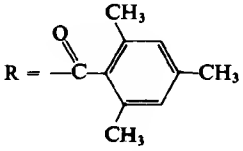
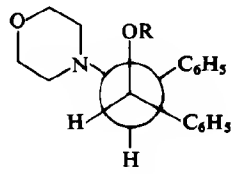


(170)

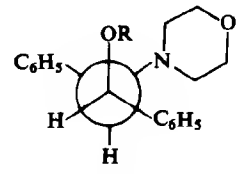
The preparation of a pair of stereoisomeric enamines to which configurations were assigned has been reported (*125*). When the mesitoate esters **171** and **172**



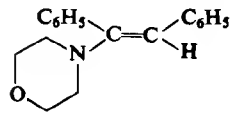
were stirred at room temperature for 3 hr in 1.5 *M* potassium *t*-butoxide in dimethyl sulfoxide, the *cis* enamine (**173**) as the major product (75%) and the *trans* enamine (**174**), respectively, were produced. The assignment of configuration was based upon the well-documented *trans* nature of a base-induced E2 elimination, the NMR spectra of the enamines and additional



(171)



(172)



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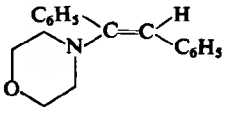
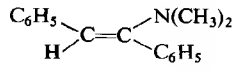


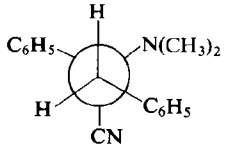
(174)

chemical and physical evidence. The *cis* enamine (**173**) is the more stable of the two, as shown by the rapid conversion of the *trans* to the *cis* isomer in a methanol solution approximately 3.5×10^{-7} *M* in boron trifluoride etherate.

An earlier report (*126*) which assigned the *trans* configuration to the enamine (**175**) derived from the cyanamine (**176**) upon reaction with potassium amide in liquid ammonia has been questioned by Munk and Kim (*125*). They also have doubts about the structures (**177** and **178**) proposed for the products obtained by the reduction of acetonitrile with sodium (*127*).

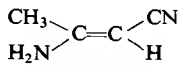


(**175**)

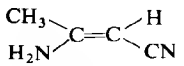


(**176**)

Careful spectroscopic (infrared and NMR) examination of these compounds should result in clarifying the structural assignments.

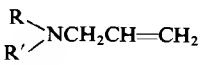


(**177**)

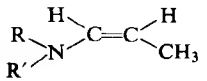


(**178**)

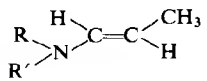
The base-catalyzed isomerization of N,N-dialkylallylamines (**179**) to a mixture of enamines consisting primarily of the *cis* isomer (**180**) has been reported (*128*). The assignments were based upon the magnitude of the



(**179**)



(**180**)

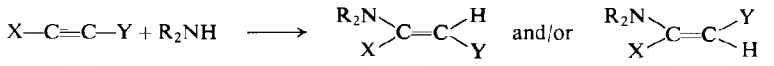


(**181**)

coupling constants for the vicinyl hydrogens [$J_{ab(trans)} > J_{ab(cis)}$]. It was also shown that enamines produced by condensation of aldehydes and secondary amines (*36*) possess the *trans* configuration (**181**). An earlier study (*129*) of the isomerization of allylamines to propenylamines also employed potassium *t*-butoxide in dimethyl sulfoxide. The infrared spectra of the enamines indicated that the *trans* isomers were produced. The discrepancy in results could be due to the facile isomerization of the *cis* enamines to the more stable *trans* forms by traces of carbon dioxide or alcohols (*128*). If Sauer and Prahl (*128*) had recorded both the NMR and infrared spectra of the *cis* enamines, more confidence could be placed in the structural assignments. In a similar study Riviere and Lattes (*129a*) showed that dehydrohalogenation of 1-(N-alkyl-N-arylamino)-2-bromopropanes gave predominantly the *trans* enamine, while isomerization of the corresponding allylamines gave the *cis* enamines as the major product.

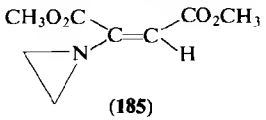
Although the emphasis in this chapter has been on the synthesis and mechanism of formation of simple enamines, brief mention will be made of the addition of amines to activated acetylenes to indicate the interest and activity in this area of substituted enamines. Since such additions tend to be stereospecific, inclusion in this section seems apropos. The addition of amines to acetylenes has been much studied (*130*), but the assigning of the stereochemistry about the newly formed double bond could not be done unequivocally until the techniques of NMR spectroscopy were well developed. In the research efforts described below, NMR spectroscopy was used to determine isomer content and to follow the progress of some of the reactions.

The general reaction may be formulated in the following way:

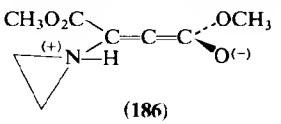


(**182**) (**183**) (**184**)

Both terminal and nonterminal acetylenes have been used. Activating groups α to the acetylenic bond have included sulfone (*131–135*), sulfoxide (*134*), ester (*28,133–139*), and ketone (*134,140*). Whether adduct **183** is designated as *cis* or *trans* depends on the investigators and the particular compound. If the addition reaction is carried out in aprotic solvents, the major isomer is **183** formed by *cis* addition (*135,138,139*). For example, the addition of aziridine to dimethyl acetylenedicarboxylate (**182**, X, Y = CO_2CH_3) in dimethyl sulfoxide (*135*) gave 75% of a mixture containing 95% of the *cis* ester **185**. Collapse of the intermediate zwitterion intermediate **186**

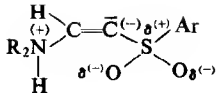


(**185**)



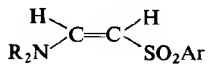
(**186**)

via intramolecular protonation would give the *cis* ester. The *trans* mode of addition can be illustrated by the reaction of a dialkylamine with *p*-tolylsulfonylacetylene (**182**, X = H, Y = *p*-$CH_3C_6H_5SO_2$) in ethanol. Truce and Brady (*133*) argue that the transition state (**187**) (Ar = *p*-$CH_3C_6H_5$) is stabilized because of electrostatic attraction (and/or attendant hydrogen-bonding forces) between the sulfonyl oxygen atoms and the positively

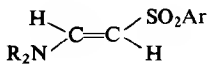


(187)

charged nitrogen. Protonation of **187** by solvent would lead to overall *trans* addition. This product (**188**) could isomerize rapidly to the more stable

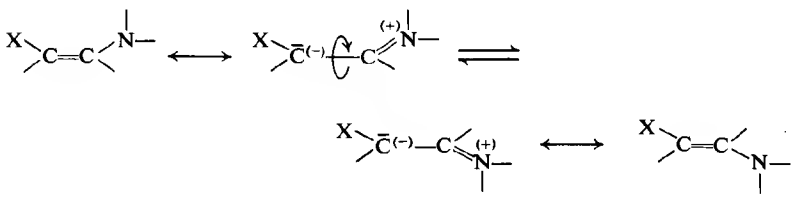


(188)



(189)

isomer (**189**) via immonium-type resonance (*133,134*). The *cis-trans* isomerization of a number of enamine β-carboxylic esters of the acetylene



series has been studied in some detail (*137*). The kinetics of the addition of aziridine, piperidine, and cyclohexylamine to methyl propiolate (**182**, X = H, Y = CO_2CH_3) and to dimethyl acetylenedicarboxylate in a variety of aprotic solvents has been undertaken (*141*). The addition reaction is second-order and the rate increases as the polarity of the solvent increases.

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3

HYDROLYSIS OF ENAMINES

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I. Introduction

Since Stork et al. introduced as a new synthetic method the alkylation and acylation of carbonyl compounds via enamines, this class of compounds has been the subject of intensive studies (*1–3*). The exceptional physical and chemical behavior of the enamine structure can be ascribed to resonance by conjugation of the unshared pair of electrons of the nitrogen atom with the π electrons of the double bond:

Electrophilic attack can occur on the β-carbon atom as well as on the nitrogen atom. The fact that enamines are basic compounds is a further characteristic property.

Hydrolysis of simple enamines appears to be very easy and decomposition to the corresponding carbonyl compound and the secondary amine can be achieved readily by adding water to these compounds. Basicity as well as

resonance may be considered as important factors which, among other effects, will determine the rate of proton addition from water. Not less important is the question of where the proton will add, on nitrogen or on the β-carbon atom. It is well known that carbon alkylation of enamines is mainly restricted to strongly electrophilic halides (*4*). The use of weakly electrophilic halides, such as primary alkyl halides, leads to the very likely irreversible formation of quaternary ammonium salts, in which the double bond is unreactive for further electrophilic attack, thus preventing the desired carbon alkylation.

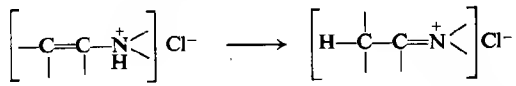
Knowledge of the mechanism enables one to obtain more insight into the various factors which determine the extent of reaction along both pathways. In this chapter special attention will be given to the kinetics and mechanism of the hydrolysis of simple enamines.†

II. Kinetics and Mechanism of the Hydrolysis of Simple Tertiary Enamines

A. Hydrolysis in Alkaline and Neutral Solution

Experimental evidence, obtained in protonation (*5,6*), acylation (*1,4*), and alkylation (*1,4,7–9*) reactions, always indicates a concurrence between electrophilic attack on the nitrogen atom and the β-carbon atom in the enamine. Concerning the nucleophilic reactivity of the β-carbon atom in enamines, Opitz and Griesinger (*10*) observed, in a study of salt formation, the following series of reactivities of the amine and carbonyl components: pyrrolidine and hexamethylene imine ≫ piperidine > morpholine > ethylbutylamine; cyclopentanone ≫ cycloheptanone; cyclooctanone > cyclohexanone; monosubstituted acetaldehyde > disubstituted acetaldehyde.

Important for the hydrolysis is the observation (*10*) that protonation of enamines with hydrogen chloride does not immediately lead to immonium salts, but in most, if not all, cases first to the formation of the corresponding enammonium ions, which afterward rearrange more or less rapidly to the more stable immonium ions [Eq. (1)]:

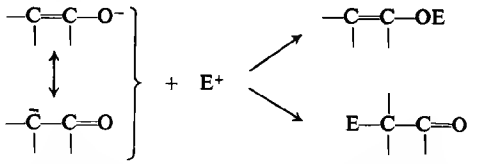


(1)

These results have led to the conclusion (*11*) that the formation of enammonium salts is kinetically controlled, while the protonation on the β-carbon atom is subject to thermodynamic control.

† Only tertiary enamines will be considered.

The same behavior has been observed in the attack of electrophiles on the ambident enolate anions, of which many reactions are closely related to those of enamines [Eq. (2)]:



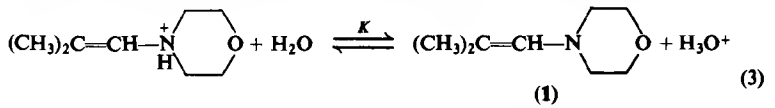
(2)

The heats of reaction for O-alkylation and C-alkylation of enolate anions clearly show that the latter reactions lead to the thermodynamically more stable products (*12*).

Hydrolysis of an enamine yields a carbonyl compound and a secondary amine. Only a few rate constants are mentioned in the literature. The rate of hydrolysis of 1-(β-styryl)piperidine and 1-(1-hexenyl)piperidine have been determined in 95% ethanol at 20°C (*13*). The values for the first-order rate constants are 4×10^{-5} sec^{-1} and approximately 10^{-3} sec^{-1}, respectively. Apart from steric effects the difference in rate may be interpreted in terms of resonance stabilization by the phenyl group on the vinyl amine structure, thus lowering the nucleophilic reactivity of the β-carbon atom of that enamine.

Recently the kinetics of the hydrolysis of 4-(2-methylpropenyl)morpholine, 1-(2-methylpropenyl)piperidine, and 1-(2-methylpropenyl)pyrrolidine have been investigated (*14,15*). Results, obtained from rate measurements of 4-(2-methylpropenyl)morpholine (**1**) in dilute phosphate buffers are shown in Fig. 1 (page 104).

The slope of the straight lines in Fig. 1 is pH-dependent. This has been explained on the ground of an equilibrium between the free enamine and the nitrogen-protonated species. This acid–base equilibrium is built up very rapidly [Eq. (3)], and causes a decrease in concentration of the reactive



(3)

(**1**)

enamine molecules immediately after the enamine is dissolved in the buffer solution. Only the fraction $K/(K + a_{H_3O^+})$ of the total amount is present as free enamine molecules.

The double bond of the nitrogen-protonated species is stable with respect to electrophilic attack under the reaction circumstances, since the free

electron pair on nitrogen is no longer available for interaction with the π electrons of the double bond. General acid catalysis has been clearly demonstrated for the hydrolysis of these enamines in the pH range 4.10 to

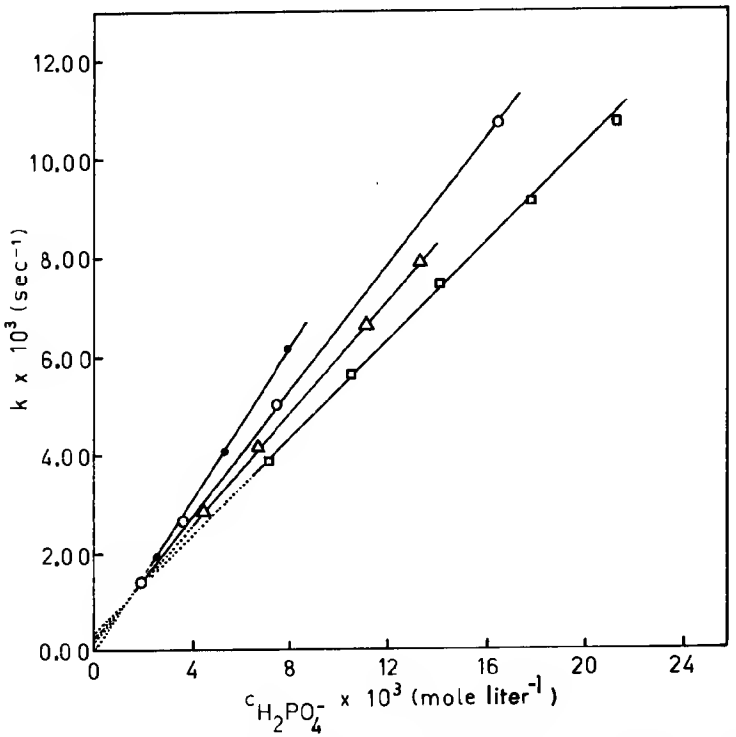


Fig. 1. First-order rate constants for the hydrolysis of 4-(2-methylpropenyl)morpholine in aqueous phosphate buffers at 25° as a function of the concentration of $H_2PO_4^-$ ions. pH values: ● 7.30; ○ 6.30; △ 6.00; □ 5.79 (*15*).

9.50. The general rate equation for the first-order ratc constants, k, is given by Eq. (4):

$$k = \frac{K}{K + a_{H_3O^+}} (k_{H_3O^+} a_{H_3O^+} + k_{HA} c_{HA} + k_{H_2O} c_{H_2O}) \qquad (4)$$

in which K is the dissociation constant of the enammonium ions in Eq. (3), and $k_{H_3O^+}$, k_{HA} and k_{H_2O} the second-order rate constants for the catalyzing agents H_3O^+, the acid component of the buffer HA, and water, respectively, only in the case of enamine **1** the contribution of the water-catalyzed

reaction is negligible. Tables 1, 2, and 3 give the values of the second-order rate constants and K values at different temperatures.

TABLE 1

Second-Order Rate Constants and Dissociation Constants of 4-(2-Methylpropenyl)Morpholine[a]

Temp., °C	$k_{H_3O^+}$, liter mole^{-1} sec^{-1}	$k_{H_2PO_4^-}$, liter mole^{-1} sec^{-1}	k_{HOAc}, liter mole^{-1} sec^{-1}	K, mole liter^{-1}
25.00	3.1×10^2	0.76	1.8	3.4×10^{-6}
39.60	9.5×10^2	—	5.4	5.8×10^{-6}
50.65	19.3×10^2	—	11.6	8.1×10^{-6}

[a] Reference (*15*).

TABLE 2

Second-Order Rate Constants and Dissociation Constants of 1-(2-Methylpropenyl)Piperidine[a]

Temp., °C	$k_{H_3O^+}$, liter mole^{-1} sec^{-1}	k_{H_2O}, liter mole^{-1} sec^{-1}	$k_{H_3BO_3}$, liter mole^{-1} sec^{-1}	K, mole liter^{-1}
25.00	0.14×10^6	0.97×10^{-5}	1.1×10^{-2}	4.4×10^{-9}
39.60	0.63×10^6	4.4×10^{-5}	4.0×10^{-2}	4.3×10^{-9}
50.24	1.8×10^6	11.3×10^{-5}	6.0×10^{-2}	3.3×10^{-9}

[a] Reference (*15*).

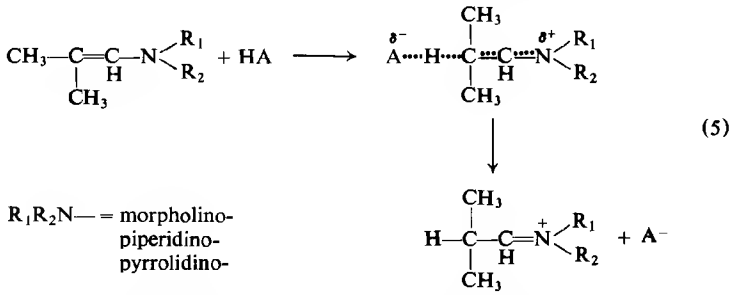
TABLE 3

Second-Order Rate Constants and Dissociation Constants of 1-(2-Methylpropenyl)Pyrrolidine[a]

Temp., °C	$k_{H_3O^+}$, liter mole^{-1} sec^{-1}	k_{H_2O}, liter mole^{-1} sec^{-1}	$k_{H_3BO_3}$, liter mole^{-1} sec^{-1}	K, mole liter^{-1}
0.00	0.69×10^6	1.2×10^{-5}	2.6×10^{-2}	1.7×10^{-9}
15.00	3.1×10^6	6.6×10^{-5}	12×10^{-2}	1.4×10^{-9}
25.00	8.4×10^6	17×10^{-5}	20×10^{-2}	1.4×10^{-9}

[a] Reference (*15*).

For this type of reaction the value of the solvent deuterium isotope effect is often a conclusive argument for the proposed mechanism (*16*). Rate measurements of **1** in acetic acid–acetate buffers in light and heavy water resulted in an isotope effect $k_{H_3O^+}/k_{D_3O^+}$ of 2.5, and k_{HOAc}/k_{DOAc} of 9. A rate-determining proton transfer to the β-carbon atom of the enamine has been proposed and accounts for the experimental results (*16–18*), Eq. (5).



(5)

R_1R_2N— = morpholino-
piperidino-
pyrrolidino-

The protonated intermediate in Eq. (5) is very reactive and could not be observed spectroscopically under the reaction circumstances. Fast hydration to isobutyraldehyde and the secondary amine occurred (*15*). This mechanism is exactly analogous to that of the hydrolysis of enolate anions (*19*), as is to be expected.

The kinetic behavior of the hydrolysis of the investigated enamines permits also a mechanism in which a nucleophilic attack on the α-carbon atom of the nitrogen-protonated enamine is the rate-determining step. However, replacement of chloride ions by perchlorate ions, of which the nucleophilicity is much smaller (*20*), has no influence on the rate, as one would expect for this mechanism. Moreover, since not acetic acid, but acetate ions are now the catalytic species in solutions of light as well as heavy water, an explanation for the large isotope effect $k_{HOAc}/k_{DOAc} = 9$ can hardly be given. This makes a rate-determining nucleophilic attack on the α carbon of enammonium ions therefore very unlikely.

It is noteworthy that the kinetics indirectly provided the evaluation of the basicities of these enamines [Eq. (4)]. The pK_a values for 4-(2-methylpropenyl)morpholine, 1-(2-methylpropenyl)piperidine, and 1-(2-methylpropenyl)pyrrolidine are 5.47, 8.35, and 8.84, respectively (*21*). Since the protonation of the β-carbon atom does not possess the character of a real equilibrium at pH 7 and up [for compound **1** even at pH 1 and up] the basicity must be fully ascribed to the equilibrium between enamine and the corresponding nitrogen-protonated conjugate acid.

B. Hydrolysis in Weakly Acidic Solution

From Eq. (4) and the data of Tables 1, 2, and 3 it can easily be calculated that the rate of hydrolysis of these enamines should rapidly reach a maximum value in weakly acidic solutions at decreasing pH, assuming that no buffer is used. The rate should then be constant and pH-independent. For enamine (**1**) Eq. (4) reduces to $k = Kk_{H_3O^+}$, and this rate must be the same as that at the intersection of the straight lines in Fig. 1. This appeared to be true for the observed rate at pH 2 (*15*).

However, at lower pH a sharp decrease in rate has been observed for 1-(2-methylpropenyl)pyrrolidine (**2**), as shown by Fig. 2, which indicates

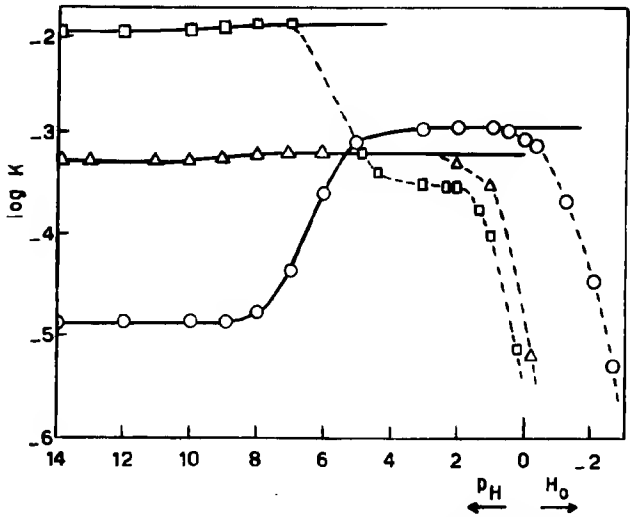


Fig. 2. Observed vs. calculated rates of hydrolysis of enamines at 24.8°. Drawn lines: calculated log k values. Observed values: ○ for 4-(2-methylpropenyl)morpholine; △ for 1-(2-methylpropenyl)piperidine; □ for 1-(2-methylpropenyl)pyrrolidine. Values are corrected for buffer contributions (*23*).

that Eq. (4) is no longer valid at lower pH values. This sudden decrease in rate cannot be explained by the mechanism proposed in Section II.A. Kinetic measurements on compound (**2**) in aqueous acetate buffers and in dilute solutions of perchloric acid have clearly demonstrated that in weakly acidic media the hydrolysis is subject to general base catalysis (Fig. 3). These results have been explained by assuming a change in rate-determining

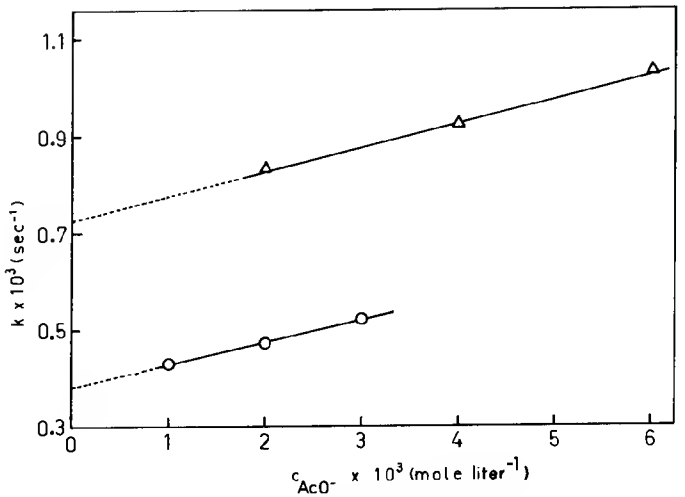


Fig. 3. First-order rate constants for the hydrolysis of 1-(2-methylpropenyl)pyrrolidine in acetate buffers (24.8°). pH values: ○, 4.41; △, 4.94 (*23*).

step from general acid-catalyzed formation of immonium ions to general base-catalyzed hydration of these ions to the amino alcohol [Eq. (6)].

$$(CH_3)_2C{=}CH{-}\overset{+}{N}H\!\!\bigcirc + H_2O \overset{K}{\rightleftharpoons} (CH_3)_2C{=}CH{-}N\!\!\bigcirc + H_3O^+ \quad \text{(a, fast)}$$

$$(CH_3)_2C{=}CH{-}N\!\!\bigcirc + H_3O^+ \underset{k_{-H_3O^+}}{\overset{k_{H_3O^+}}{\rightleftharpoons}} (CH_3)_2CH{-}CH{=}\overset{+}{N}\!\!\bigcirc + H_2O \quad \text{(b, fast)}$$

$$(CH_3)_2CH{-}CH{=}\overset{+}{N}\!\!\bigcirc + H_2O + B \xrightarrow{k_B} (CH_3)_2CH{-}\underset{OH}{CH}{-}N\!\!\bigcirc + HB^+ \quad \text{(c, slow)} \qquad (6)$$

The observed first-order rate constant of the overall reaction is

$$k = \frac{Kk_{H_3O^+}\, a_{H_3O^+}}{Kk_{H_3O^+}\, a_{H_3O^+} + Kk_{-H_3O^+} + k_{-H_3O^+}\, a_{H_3O^+}} \cdot \sum_i k_{B_i}\, c_{B_i} \qquad (7)$$

In the pH range of interest $Kk_{-H_3O^+} \ll k_{-H_3O^+} a_{H_3O^+}$ (see Table 3). From observations of Opitz and Griesinger in the rearrangement of tertiary

enammonium salts in immonium salts (10) and from NMR spectra of enamine **1** in perchloric acid solution (*23*) it may be concluded that as soon as the reactions of Eqs. (6a) and (6b) have reached equilibrium, the concentration of enammonium ions may be neglected with regard to the concentration of immonium ions. Therefore Eq. (7) reduces to

$$k = \sum_i k_{B_i}\, c_{B_i} \qquad (8)$$

At pH values lower than 4 the concentration of hydroxide ions becomes too small to give an appreciable contribution to the overall rate and only water acts as the catalyzing base (Fig. 2). In this pH range the rate is, therefore, pH-independent, as is predicted from the data of Table 4.

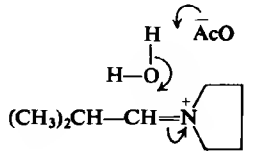
TABLE 4

Second-Order Rate Constants for the Hydrolysis of Immonium Ions, Derived from 1-(2-Methylpropenyl)Pyrrolidine at 24.8°C[a]

k_{OH^-}, liter mole^{-1} sec^{-1}	k_{OAc^-}, liter mole^{-1} sec^{-1}	k_{H_2O}, liter mole^{-1} sec^{-1}
4×10^5	4×10^{-2}	5.5×10^{-6}

[a] Reference (*23*).

Direct attack of acetate ions on the α-carbon atom of the immonium ions in the acetate buffer solutions is unlikely, but the catalyzing action involves the removal of a proton from a water molecule in its attack on the immonium ion.

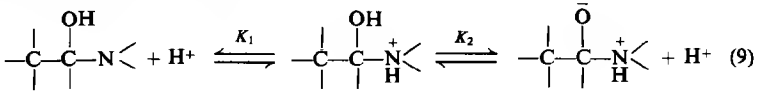


A similar concerted mechanism accounts for the water-catalyzed reaction, which becomes predominant at pH values lower than 4. The transition in rate-determining step has not been observed for the other two enamines. This point will meet attention in Section III.

It is interesting to note that the hydrolysis of certain Schiff bases in weakly acidic solutions shows a similar mechanism (*22*). N-protonated substituted benzylidene-*t*-butylamines react with hydroxide ions to amino alcohols in the rate-determining step, and at lower pH the rate is almost entirely determined by attack of water on the protonated Schiff bases as a consequence of the rapidly decreasing concentration of hydroxide ions.

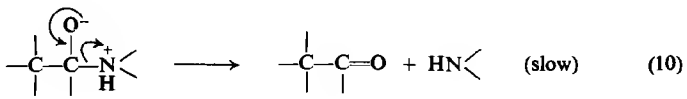
C. Hydrolysis in Strongly Acidic Solution

The rate of hydrolysis of 4-(2-methylpropenyl)morpholine, 1-(2-methylpropenyl)piperidine, and 1-(2-methylpropenyl)pyrrolidine decreases sharply around pH 0 (Fig. 2). Such a decrease in rate is not to be expected on basis of Eq. (4), which predicts a constant and pH-independent rate at lower pH values. Obviously Eq. (4) is no longer valid for any of the three enamines in strongly acidic solution. Since the kinetics of the hydrolysis of the last-mentioned enamine show a rate-determining formation of the intermediate amino alcohol, the formation of which becomes pH-independent around pH 2, it is evident that a further decrease in rate at still lower pH indicates another change in the rate-determining step. A slow decomposition of the amino alcohol to isobutyraldehyde and secondary amine has been proposed as this accounts for the sharp decrease in rate at pH 0 (*23*). The amino alcohol, to a large extent nitrogen-protonated in acidic media, is in rapid equilibrium with the uncharged derivative and the dipolar structure [Eq. (9)].



(9)

It has been concluded from an estimate of K_1 and K_2 that the uncharged amino alcohol as well as the dipolar structure are present in small concentrations (*24*). The decomposition is strongly retarded as the pH is lowered and this phenomenon has been explained by assuming the zwitterions to be the active intermediates [Eq. (10)].

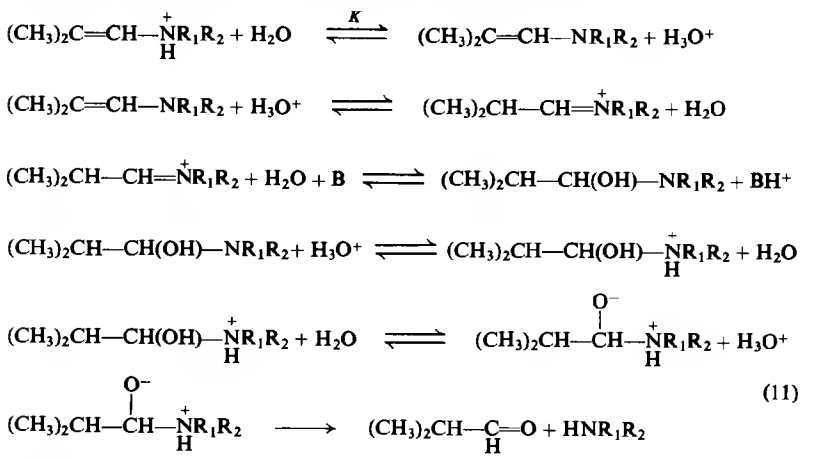


(10)

A strong argument in favor of the proposed mechanism (*23*) over other possible reaction pathways is that the enhanced driving force, present in the

ammonium alcoholate ion, is necessary to expel the strongly basic amine. The kinetics of the hydrolysis of Schiff bases, derived from strongly basic amines, if carried out under acidic conditions, have been explained to occur also via similar dipolar intermediates (*22*). The slow decomposition of the zwitterion is an uncatalyzed reaction. This is supported by the observation that isobutyraldehyde reacts rapidly with strongly secondary amines to amino alcohols without the aid of acid catalysts (*25*).

The proposed mechanism indicates that all the foregoing reactions in the sequence are now more or less rapidly established equilibria and the complete reaction scheme can be written as shown in Eq. (11).



(11)

HNR_1R_2 = morpholine
piperidine
pyrrolidine

The concentrations of the different intermediates are determined by the equilibrium constants. The observation of immonium ions [Eq. (5)] in strongly acidic solutions by ultraviolet and NMR spectroscopy also indicates that these equilibria really exist (*23,26*). The equilibria in aqueous solutions are of synthetic interest and explain the convenient method for the preparation of 2-deuterated ketones and aldehydes by hydrolysis of enamines in heavy water (*27*).

It has been noticed that the reverse reaction of Eq. (5) is a particular type of the Hofmann elimination reaction (*26*) via either an E2 or an E1cB mechanism. An E2 mechanism seems to be more obvious for this reaction than an E1cB mechanism, however.

Finally, it should be noted that at alkaline and neutral pH a concerted mechanism, involving β-carbon protonation of the enamine and a simultaneous addition of a water molecule, leading to the amino alcohol, can be rejected, since the immonium ion appeared to be a real and detectable intermediate.

III. Structure and Reactivity

The hydrolysis of enamines proceeds via a number of separate reactions, which may be considered as equilibria. Which reaction in the sequence becomes rate-determining depends on the pH of the solution as well as on the structure of the intermediates. Under alkaline and neutral conditions the order of reactivity of the enamines discussed in the foregoing sections is: pyrrolidino- > piperidino- > morpholino-. One would expect the rate of protonation in the first step to be strongly dependent on the basicity of the enamine. This is true for the morpholino and piperidino enamines, but the much higher protonation rate of the pyrrolidino enamine in comparison with the piperidino compound, of which the basicities are closely similar, cannot be explained in this way. The tendency of the five-membered ring of the amine part in the molecule to form an energetically favorable exocyclic double bond accounts for the much higher reactivity of this enamine than the corresponding piperidino enamine and has been observed in a large number of electrophilic addition reactions (*2,4*).

Notwithstanding the expected and also observed high reactivity of the intermediate immonium ions, the stabilization of the exocyclic double bond in the pyrrolidino derivative evidently prevents rapid nucleophilic attack of water and the hydration of this ion to the amino alcohol becomes a slow general base-catalyzed process in weakly acidic solutions [Eq. (6)].

The difference in reaction rates of the amino alcohols to isobutyraldehyde and the secondary amine in strong acidic solutions is determined by the reactivity as well as the concentration of the intermediate zwitterions [Fig. 2, Eq. (10)]. Since several of the equilibrium constants of the foregoing reactions are unknown, an estimate of the relative concentrations of these dipolar species is difficult. As far as the reactivity is concerned, the rate of decomposition is expected to be higher, according as the basicity of the secondary amines is lower, since the necessary driving force to expel the amine will increase with increasing basicity of the secondary amine. The kinetics and mechanism of the hydrolysis of enamines demonstrate that not only resonance in the starting material is an important factor [e.g., if resonance is eliminated by steric hindrance, as in dehydroquinuclidine (*28*), hydrolysis is practically impossible], but the position of the equilibria as well as the rates are also affected by inductive and steric substituent effects.

ACKNOWLEDGMENT

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4

ELECTROPHILIC SUBSTITUTIONS AND ADDITIONS TO ENAMINES

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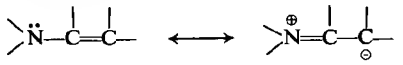
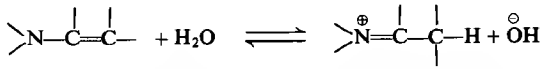
I. General Comments

Enamines have a three-atom π system and are thus in principle capable of reaction with an electrophile on nitrogen or on carbon as shown by the mesomeric forms (**1**) and (**2**).



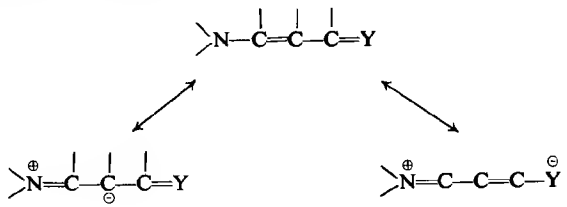
(**1**) (**2**)

It might also be expected that enamines would be less basic than the corresponding saturated tertiary amines as a consequence of the delocalization of the nonbonded electron pair of the nitrogen. The older literature (*1–4*), which involved measurements in aqueous or partly aqueous solution, led to the opposite conclusion. This unexpected increase in basicity was rationalized in terms of an equilibrium between the enamine and the quaternary iminium hydroxide:



Recent work (*5*) using kinetic methods has shown that the enamines derived from isobutyraldehyde are indeed less basic than the corresponding saturated tertiary amines.

If the conjugation of the enamine system is extended, a third site of reaction becomes possible.



(**3**)

The basicity of the nitrogen is further reduced when Y is an electron-attracting atom such as an oxygen, and the mesomeric form (**3**) becomes increasingly important.

The above considerations presuppose that two important conditions are fulfilled. First the nitrogen must be tertiary, as primary and secondary vinylamines are generally more stable in the imine form (*6*). Only in the case of enamino ketones and esters are the enamine more stable than the imine forms (*7*). Secondly, the atoms comprising the π system must be able

to lie in the same plane, as otherwise full interaction of the nonbonded electrons on nitrogen with the π electrons of the double bonds is not possible. Such steric inhibition of mesomerism occurs mainly in polycyclic systems, and in extreme cases such systems do not show the properties characteristic of enamines (*8,9*).

II. Protonation

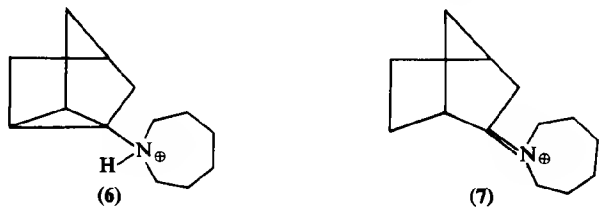
In the case of enamines protonation on nitrogen or carbon is possible and gives the conjugate acids **4** and **5**, respectively. Whereas the final isolated product has the iminium salt structure (**5**), recent work (*10–12*) has shown

(**4**) (**5**)

that protonation takes place rapidly on nitrogen and is followed by a relatively slow transfer of the proton to the carbon.

The structure of the protonated enamines has been investigated by infrared spectroscopy. On protonation there is a characteristic shift of the band in the double-bond stretching region to higher frequencies by 20 to 50 cm^{-1} with an increased intensity of absorption (*6,13,14a*). Protonated enamines also show absorption in the ultraviolet at 220–225 mμ due to the iminium structure (*14b*). This confirms structure **5** for these protonated enamines, because a compound having structure **4** would be expected to have only end absorption as the electrons on nitrogen would not be available for interaction with the π electrons of the double bond.

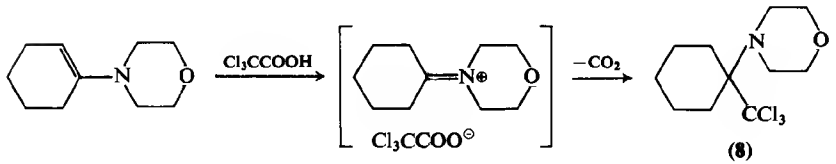
The above assumes that C protonation is not excluded for steric reasons. Thus N protonation takes place with derivatives of dehydroquinuclidine and the alkaloids neostrychnine and trimethylconkurchine (*8*). N protonation was also believed to occur in the case of 2-N-hexamethyleneimino-bicyclo[1,2,2]-2-heptene, which was believed to give the nortricyclene derivative (**6**) on protonation with perchloric acid. Later work, however, showed the salt to be the results of C protonation (*15*) and to have structure **7**.



(**6**) (**7**)

For purposes of characterization of enamines the perchlorate salts are preferred, as they crystallize well, and the perchlorate anion has no tendency to add to the iminium cation. Other salts, including hexachlorostannates (*13*), hexachloroantimonates (*13*), chlorides, bromides, tetraphenylborates, and nitrates, have also been used. Recently a method for the preparation of iminium salts directly from aldehydes or ketones and the amine perchlorate has been reported (*16*).

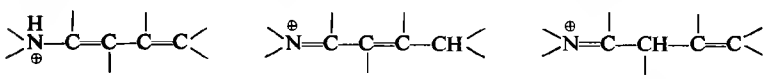
When trichloroacetic acid is used to protonate an enamine (*17,17a*), the salt has only limited stability. The trichloroacetate anion undergoes decarboxylation and the trichloromethyl anion which is generated adds to the iminium salt, giving an α-amino trichloromethyl derivative (**8**).



(**8**)

The iminium salts are of course especially subject to attack by nucleophiles, and reactions of this type are discussed in Chapter 5. See also Section V.H.

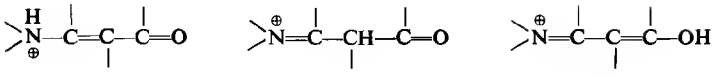
In the case of dienamines an additional site becomes available for protonation and three conjugate acids **9**, **10**, and **11** are possible. Evidence available suggests that although protonation with mineral acids gives the protonated form (**10**) as the final product, the latter is the result of rearrangement of an



(**9**) (**10**) (**11**)

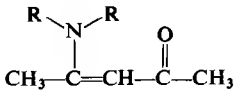
initial N-protonated salt (*18*). In protonation with organic acids the products have structure **11** with isolated double bonds presumably formed by direct protonation of carbon in the middle of the dienamine system (*19*). Similar results have been observed in the protonation of steroidal dienamines with mineral acids (*20*).

Enamino ketones can protonate not only on nitrogen or carbon but also on oxygen to give **12**, **13**, and **14**, respectively. Enamino ketones form stable perchlorates, chlorides, bromides, and iodides, and examination of their infrared (*21,22*), ultraviolet (*23*), and nuclear magnetic resonance (*24,25*) spectra show these salts to be O protonated. The salts of 4-dialkylamino-



(**12**) (**13**) (**14**)

pent-3-en-2-one (**15**), which were believed to be either N or C protonated (*21*), have recently been shown to be O protonated by both ultraviolet (*23*) and nuclear magnetic resonance spectral data (*24*).



(**15**)

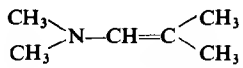
III. Alkylation

Alkylation of enamines can take place on carbon or on nitrogen (see Section I). The theoretical considerations and reaction conditions which determine whether C or N alkylation takes place have already been studied extensively (*26–32*). These studies have shown that the facility with which alkylation takes place depends on the basicity of the enamine, on the ease of formation of a trigonal atom in the transition state, and on the nature of the enamine, the alkylating agent, and the solvent.

A. Reaction with Alkyl Halides

Because of self-condensation under the conditions of the alkylation reaction, enamines derived from acetaldehyde or monosubstituted acetaldehydes cannot usually be alkylated (*28*); except when there is a bulky secondary amine used to produce the enamine (*32a*). In these cases C alkylation takes place in good yield.

Enamines derived from aldehydes disubstituted on the β carbon such as those derived from isobutyraldehyde (**16**) are alkylated on nitrogen by alkyl

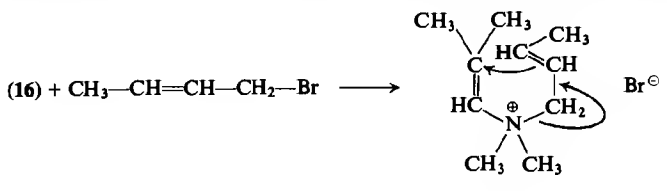


(**16**)

halides (*28*). In alkylations of these compounds by allyl or benzyl halides the products are those of C alkylation (*33,34*).

The C alkylation has been rationalized (*33*) by initial N alkylation of **16** to **17** followed by an intramolecular rearrangement involving a six-membered

cyclic transition state to the intermediate **18**, which on hydrolysis gave 2,2,3-trimethyl-4-pentenal (**19**). Support for this mechanism was provided



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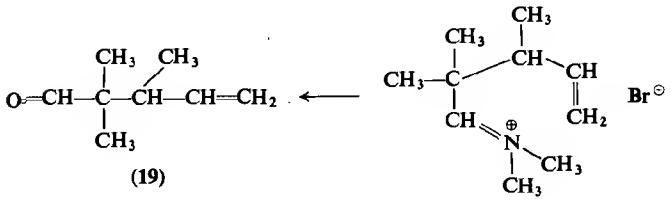
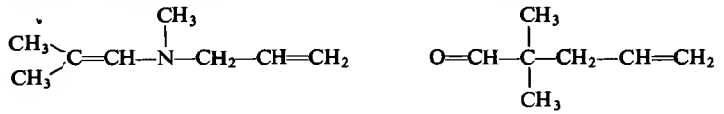


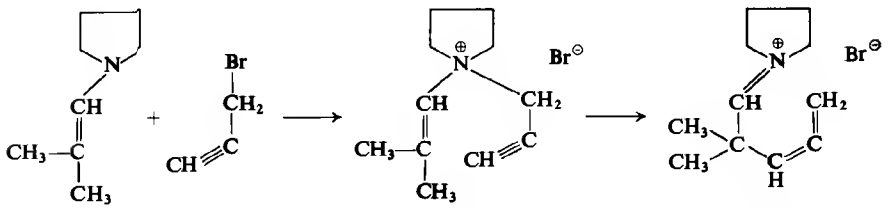
(19) (18)

by the alkylation of 2-N-dimethyl-N-(2-propenyl)-1-propene (**20**) by methyl tosylate, which on hydrolysis gave 2,2-dimethyl-4-pentenal (**21**).



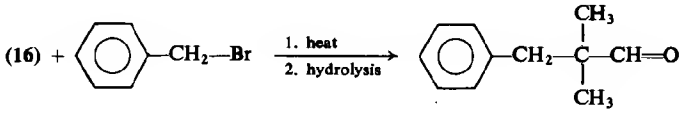
(20) (21)

Similarly alkylation (*35*) of 1-N-pyrrolidino-2-methyl-1-propene (**22**) with propargyl bromide gave initial N alkylation to (**23**) with subsequent rearrangement to the allene (**24**).



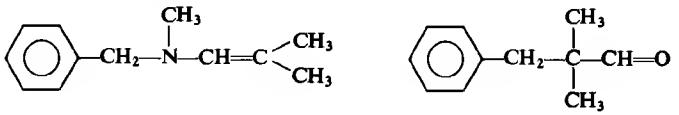
(22) (23) (24)

N Alkylation of **16** with benzyl bromide also occurs, and further heating of the reaction mixture leads to the C-alkylated product (**25**), probably by an intermolecular mechanism (*33*).



(25)

Support for initial N alkylation is provided by the reaction of N-isobutenyl-N-methylbenzylamine (**26**) with methyl iodide, which gave α,α-dimethylhydrocinnamaldehyde (**27**) on hydrolysis (*33*).



(26) (27)

When N alkylation is not possible for steric reasons, C alkylation appears to occur directly (*35*). Solvents of high dielectric also favor C alkylation *27,29*). Thus 1-N-pyrrolidino-2-methyl-1-propene (**22**) with allyl bromide in ether gave only 20% of C-alkylated product, while in acetonitrile over 50% of this product is obtained.

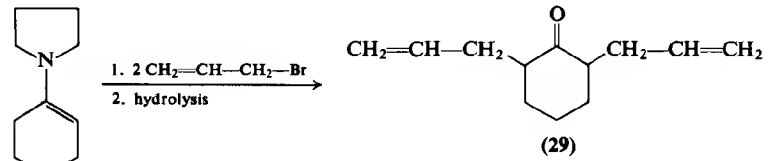
With enamines of cyclic ketones direct C alkylation occurs with allyl and propargyl as well as alkyl halides. The reaction is again sensitive to the polarity of the solvent (*29*). The pyrrolidine enamine of cyclohexanone on reaction with ethyl iodide in dioxane gave 25% of 2-ethylcyclohexanone on hydrolysis, while in chloroform the yield was increased to 32%.

The course of alkylation is also influenced by the steric arrangement of the enamine. 1-Pyrrolidino-1-cycloheptene gave approximately equal quantities of the C- and N-alkylated products in dioxane, while 1-pyrrolidino-1-cyclooctene, and 1-pyrrolidino-1-cyclononene afforded N-alkylated products exclusively under similar conditions (*29*). The reason for N alkylation in the eight- and nine-membered ring compounds is to be found in the conformation of these rings, which prevents full interaction of the unshared electrons on nitrogen with the π electrons of the double bond.

Enamines prepared from the more basic amines are alkylated more easily and in higher yield, but yields are also affected by the ease of formation of an exocyclic double bond in the transition state (*32*). Thus the enamines derived

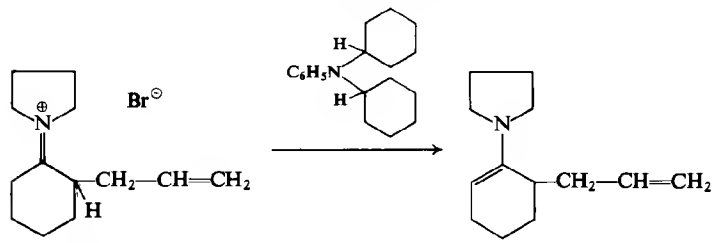
from cyclohexanone and piperidine, which is as strong a base as pyrrolidine, nevertheless give lower yields.

One of the advantages of the enamine alkylation reaction over direct alkylation of the ketone under the influence of strong base is that the major product is the monoalkylated derivative (*29,32*). When dialkylation is observed, it occurs at the least substituted carbon in contrast to alkylation with base, where the α-disubstituted product is formed. Dialkylation becomes the predominant reaction when a strong organic base is added and an excess of alkyl halide is used (*29*). Thus 1-N-pyrrolidino-1-cyclohexene (**28**) on treatment with two moles of allyl bromide in the presence of ethyl dicyclohexylamine (a strong organic base which is not alkylated under the reaction conditions) gave a 95% yield of 2,6-diallylcyclohexanone (**29**).



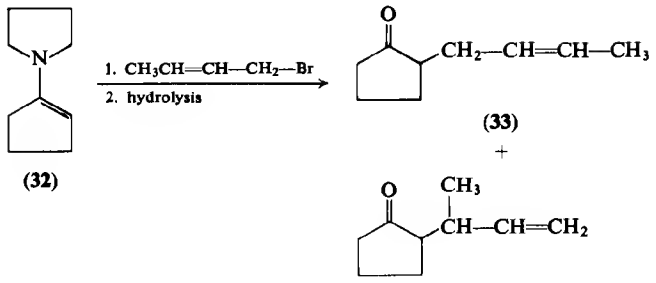
(**28**) (**29**)

The course of the reaction appears to involve dehydrohalogenation of the intermediate iminium salt (**30**) to the new enamine (**31**), which then undergoes further alkylation. Evidence that alkylation in this case is directly on



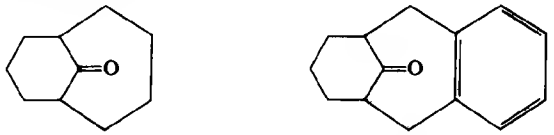
(**30**) (**31**)

carbon (*29*) rather than on nitrogen (*35*) followed by a rearrangement to carbon as in the case of the aldehyde enamines is provided by the alkylation of 1-N-pyrrolidino-1-cyclopentene (**32**). Alkylation of (**32**) with crotyl bromide followed by hydrolysis gave more than 80% of the 2-crotyl cyclopentanone (**33**) and less than 20% of the 2-(α-methyl allyl)cyclopentanone (**34**).



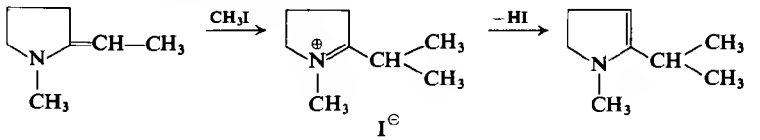
(**32**)

The 2,2′-dialkylation of enamines has been used for the synthesis of novel bi- and tricycloketones (*36*). Alkylation of 1-N-pyrrolidino-1-cyclohexene (**28**) with 1,4-diiodobutane gave a 15% yield of bicyclo[1.3.4]-10-decanone (**35**), while alkylation with *o*-xylylenedibromide gave a 31% yield of 2,6-*o*-xylylenecyclohexanone (**36**).



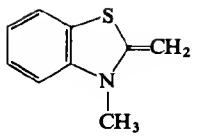
(**35**) (**36**)

The first example of an enamine alkylation reaction was the conversion of 1,3,3-trimethyl-2-methyleneindoline, the so-called Fisher's base, which was shown to give 1,3,3-trimethyl-2-isopropylideneindoline with methyl iodide rather than a quaternary salt (*37,38*). More recently other heterocyclic enamines have been shown to undergo similar reactions. Thus 1-methyl-2-ethylidenepyrrolidine (**37**) gave the iminium salt (**38**) on alkylation with methyl iodide (*39*). The latter then loses hydrogen iodide to give 1-methyl-2-isopropyl-2-pyrroline (**39**).



(**37**) (**38**) (**39**)

In the benzothiazole series there was some confusion in the literature as the simplest enamine (**40**) exists as the dimer (**41**) (*40*). The dimer undergoes alkylation on sulfur (*41*) rather than at the "enamine" carbon of **41**.



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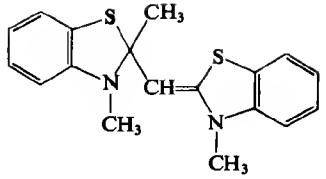
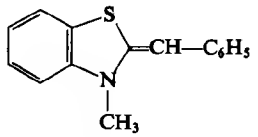
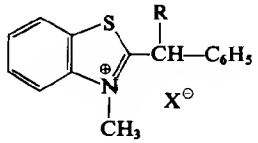


(41)

However, it has recently been shown (*42*) that monomeric enamines such as **42** react normally to give the benzothiazoline salt (**43**) on alkylation with alkyl and benzyl halides.

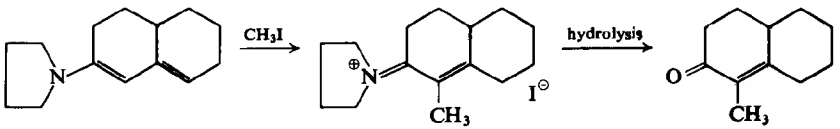


(42)



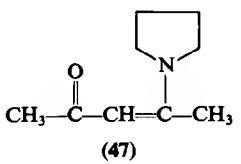
(43)

The alkylation of dienamines has not been studied extensively. Thus the dienamine (**44**) is reported (*43,44*) to alkylate at C_2 with methyl iodide to give the iminium salt (**45**), which on hydrolysis gives the alkylated α,β-unsaturated ketone (**46**). Similar dienamines prepared from Δ^4-3-oxo steroids, on the other hand, are reported to undergo only N alkylation (*45*).

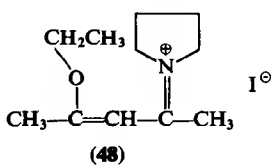


(44) (45) (46)

Alkylation of enamino ketones occurs on oxygen, as would be expected from the site of protonation. Thus 4-N-pyrrolidino-3-penten-2-one (**47**) gave N-(2-ethoxy-2-penten-4-ylidene)-pyrrolidinium iodide (**48**) on alkylation with ethyl iodide (*22*), and the enamino ketones derived from 5,5-

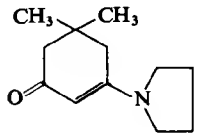


(47)



(48)

dimethylcyclohexane-1,3-dione and pyrrolidine (**49**) or morpholine (**50**) gave the corresponding O-alkylated salts (**51**) on treatment with methyl iodide (*22,46*).



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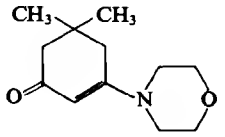

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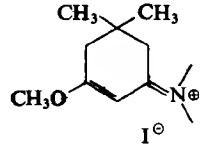
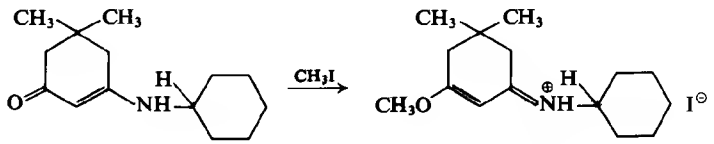


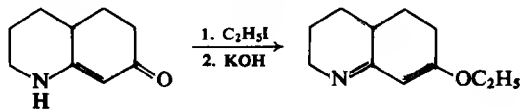
(51)

Even 5,5-dimethyl-3-cyclohexylaminocyclohex-2-en-1-one (**52**), the mono-Schiff's base derived from the 1,3-diketone which is stable in the enamino ketone form (*7*) and theoretically could alkylate on nitrogen, gave the O-alkylated product (**53**) (*23*).



(52) (53)

In a similar manner it was shown (*47*) that the enamino ketone (**54**) on treatment with ethyl iodide gave an intermediate hydroiodide from which 7-ethoxy-2,3,4,5,6,10-hexahydroquinoline (**55**) was obtained on treatment with base. The corresponding N-alkylated product was obtained by alkylation of (**54**) in the presence of sodium hydride.

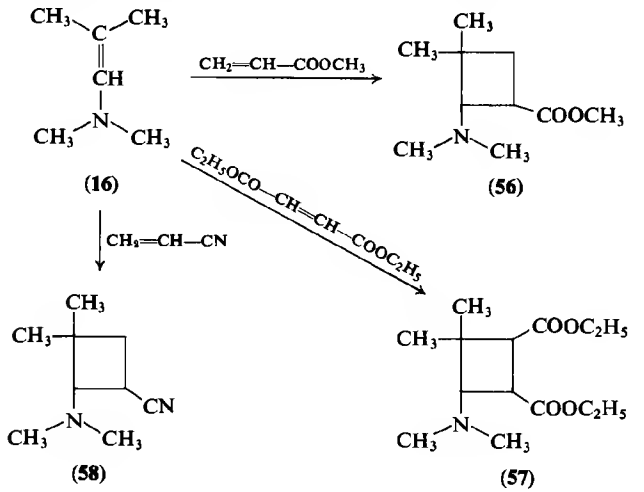


(54) (55)

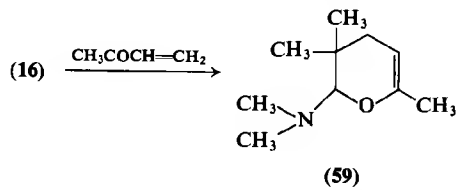
B. Reaction with Electrophilic Olefins

Enamines are readily alkylated by olefins activated by electron-withdrawing substituents. N Alkylation by one of these olefins is reversible, whereas C alkylation is not, so that a good yield of monoalkylated product is the rule.

In the case of enamines derived from aldehydes a cycloaddition to give a cyclobutane occurs (*48–50*). Thus the enamine (**16**) reacted with methyl acrylate in acetonitrile to give a 91% yield of methyl 2-dimethylamino-3,3-dimethylcyclobutane carboxylate (**56**). Similarly, treatment of (**16**) with diethylmaleate at 170° gave a 70% yield of diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (**57**), and **16** and acrylonitrile gave a 65% yield of 2-dimethylamino-3,3-dimethylcyclobutanecarbonitrile (**58**).

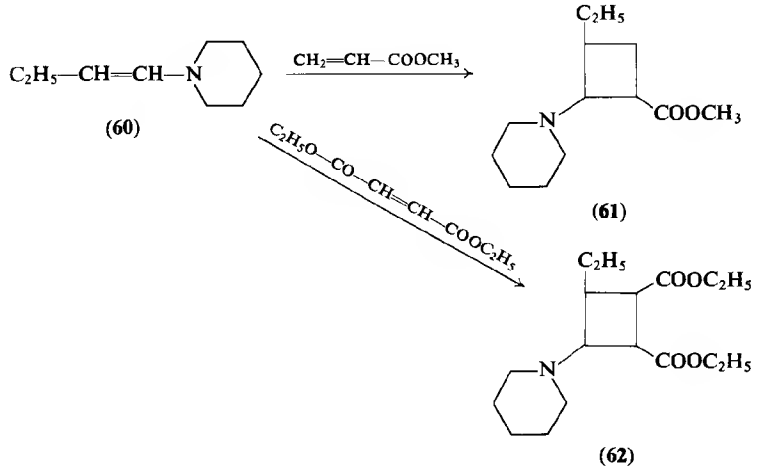


Similar cycloaddition reactions were observed with methyl vinyl sulfone (*48*) and β-nitrostyrene (*48,51*). Methyl vinyl ketone, on the other hand, is reported to give dihydropyrans as the initial products (*50,52,53*). Thus (**16**) on reaction with methyl vinyl ketone at room temperature for 12 hr gave a 60% yield of 2-dimethylamino-3,3,6-trimethyl-3,4-dihydro-2H-pyran (**59**).



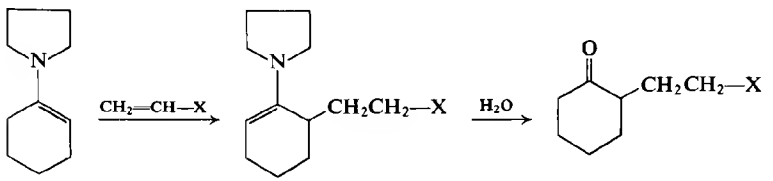
Enamines having a hydrogen on the enamine carbon also undergo cycloaddition to give cyclobutane derivatives. The latter are less stable, so that the reaction must be carried out under milder conditions in order to obtain

products (*48*). The piperidine enamine of butyraldehyde (**60**) on reaction with methyl acrylate gave methyl 2-(N-piperidino)-3-ethylcyclobutanecarboxylate (**61**) in 83% yield when the reaction was carried out in acetonitrile for 2 days at room temperature. Similar reaction of **60** with diethyl maleate gave the cyclobutane derivative (**62**) in 45% yield.

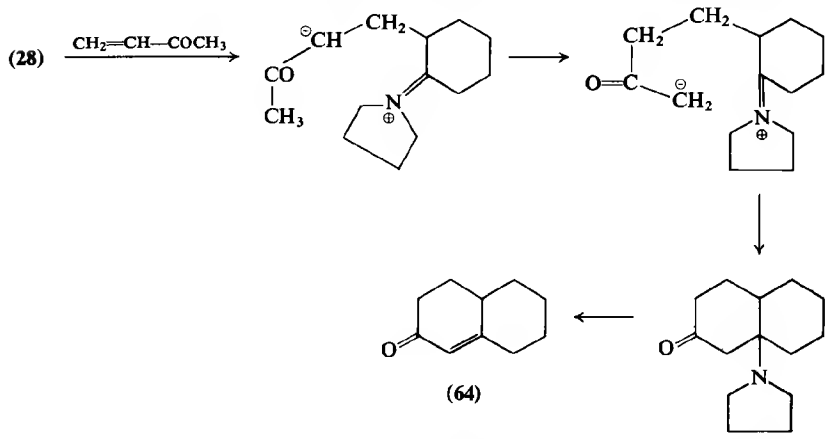


The simple addition of acrolein to enamines derived from aldehydes to give substituted glutardialdehydes has also been observed (*54*).

The enamines derived from cyclic ketones give the normal alkylated products, although there is some evidence that unstable cycloadducts are initially formed (*55b*). Thus the enamine (**28**) derived from cyclohexanone and pyrrolidine on reaction with acrylonitrile, acrylate esters, or phenyl vinyl sulfone gave the 2-alkylated cyclohexanones (**63**) on hydrolysis of the intermediates (*31,32,55,56*). These additions are sensitive to the polarity of the solvent. Thus (**28**) in benzene or dioxane gave an 80% yield of the

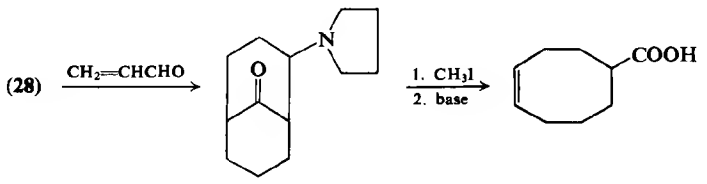


monoalkylated product (**63**) with acrylonitrile, whereas in ethanol the 2,6-dialkylated product predominated (*31,32*). When alkylation of the enamine **28** is carried out with an olefin having a reactive carbonyl group present, further condensation frequently occurs (*32*). Methyl vinyl ketone reacts with **28** to give an adduct which undergoes cyclization under the influence of acetic acid and sodium acetate in water to give the octalone (**64**).



(64)

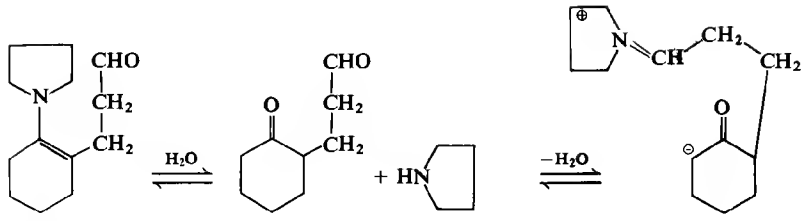
Alkylation of **28** with acrolein gives the bicyclic ketone (**65**), which can be converted to 4-cyclooctene-1-carboxylic acid by the action of base on its methiodide (*55a*).



(65)

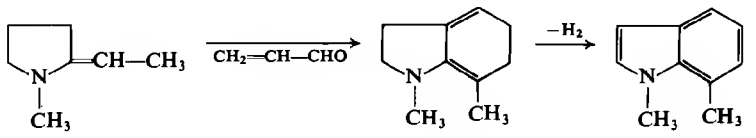
The formation of **65** must have taken place via the normal alkylation product (**66**) which undergoes hydrolysis with water followed by reaction of pyrrolidine with the more reactive aldehyde group to give an intermediate (**67**), which can then cyclize to give the observed product (**65**).

The addition of ethyl acrylate to both possible enamine structures of 1,2-dimethyl-Δ^2-piperideine (*57*), 1-methyl-2-ethyl-Δ^2-piperideine (*58*) and 1,2-dimethyl-Δ^2-pyrroline (*59*) has been demonstrated and is sometimes



(66) (67)

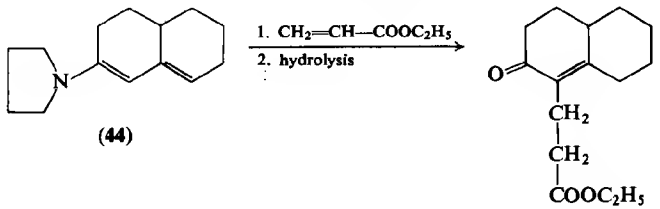
accompanied by an intramolecular acylation by the ester group to give cyclic enamino ketones (*60*). The addition (*61*) of acrolein to 1-methyl-2-ethylidene pyrrolidine (**68**) led to the adduct (**69**), which was dehydrogenated to 1,7-dimethylindole (**70**).



(68) (69) (70)

The reaction of enamines with perfluoro olefins has also been reported (*62*).

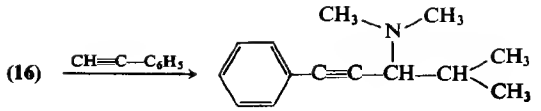
Dienamines have been reported to react with ethyl acrylate at C_2 to give the alkylated α,β-unsaturated ketone derivative. Thus the dienamine (**44**) gave **71** in 50% yield on reaction with ethyl acrylate in dioxane for 40 hr (*63*).



(44) (71)

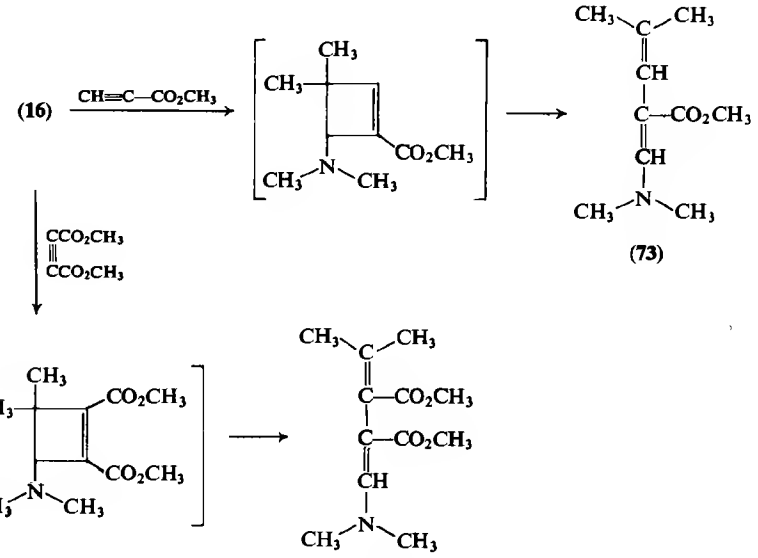
C. Reaction with Acetylenes

Nonactivated terminal acetylenes have been added to enamines derived from aldehydes. A long reaction time or catalysis by copper(I) chloride is necessary. Thus the enamine (**16**) formed the adduct (**72**) on heating with phenylacetylene (*64*).



(72)

A more conventional cycloaddition occurs with activated acetylenes, however, the intermediate cyclobutene adducts undergo rearrangement to give insertion of two carbon atoms into the enamine chain (*65*). Thus the enamine (**16**) reacted with methyl propiolate to give the dienamino ester (**73**), presumably via the cycloaddition product (*65a*).



(73)

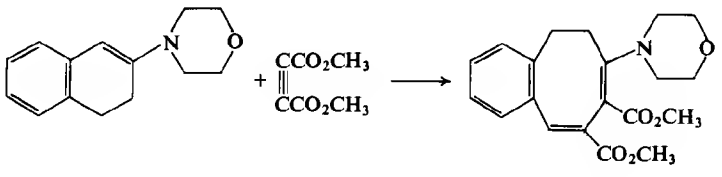
(74)

Dimethyl acetylenedicarboxylate reacts similarly to give **74**. Again the cycloaddition is presumed to be the initial step (*65b*).

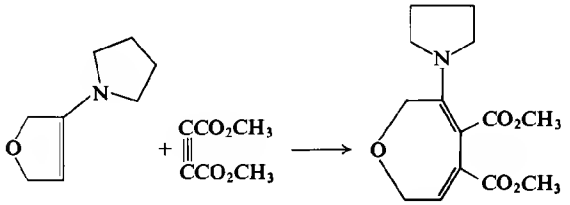
A similar sequence of reactions takes place with the enamines of cyclic ketones (*65–67*); the initially formed unstable cyclobutene rearranges with insertion of two carbon atoms into the ring. A wide variety of cyclic ketones have been allowed to react in this way. For instance, the enamine (**75**) gave **76** on reaction with dimethyl acetylenedicarboxylate in refluxing toluene (*66*) and the heterocyclic enamine (**77**) obtained from dihydro-3-(2H)-

furanone, and dimethyl acetylenedicarboxylate gave dimethyl 2,7-dihydro-3-pyrrolidienyl-4,5-oxepindicarboxylate (**78**) at room temperature in ether (*65b*).

Enamino ketones and esters also react with dimethyl acetylenedicarboxylate (*67*). Again cycloaddition appears to occur and the unstable cyclobutene intermediates rearrange to give insertion of two carbon atoms.

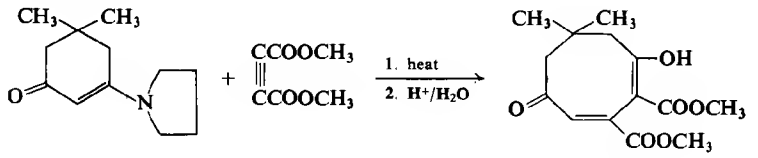


(75) (76)



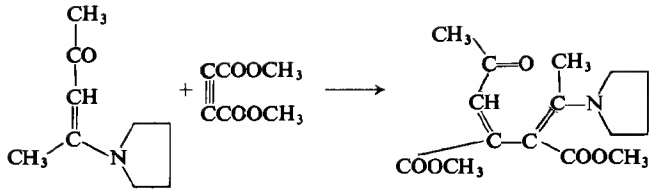
(77) (78)

The enamino ketone 5,5-dimethyl-1-pyrrolidinocyclohex-1-en-3-one (**49**) on treatment with dimethyl acetylenedicarboxylate and subsequent hydrolysis yielded 2,3-dicarbomethoxy-7,7-dimethyl-1-hydroxy-5-oxo-1,3-cyclooctadiene (**79**).



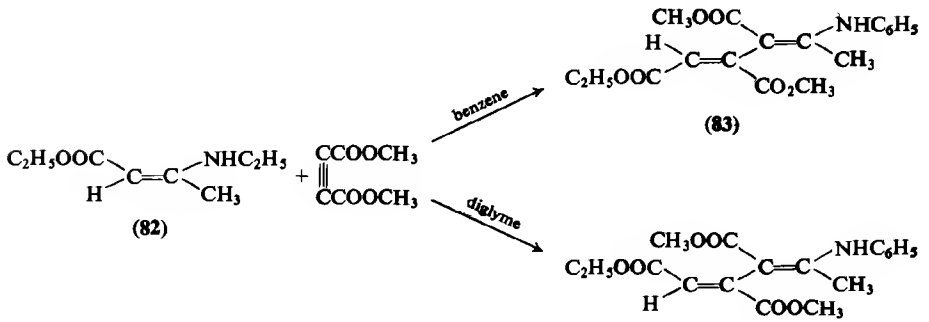
(49) (79)

A particularly interesting case is the reaction of the enamino ketone (**47**), which under similar conditions gives the intermediate product (**80**), which then undergoes cyclization to the benzene derivative dimethyl 3-pyrrolidino-5-methyl phthalate (**81**).



(47) (80) (81)

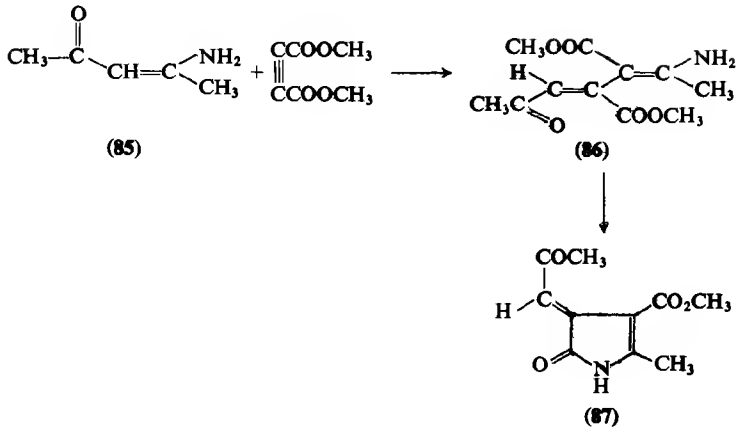
Ethyl 3-anilinocrotonate (**82**) undergoes reaction with dimethyl acetylenedicarboxylate (*67*) with the formation of two products, ethyl 5-anilino-3,4-dicarbomethoxy-*trans,cis*-2,4-hexadienoate (**83**) and ethyl 5-anilino-3,4-dicarbomethoxy-*cis,cis*-2,4-hexadienoate (**84**).



(82) (83) (84)

In benzene, **83** is the major product, while in diglyme at 85°, **84** predominates.

It is interesting to note that 4-aminopent-3-en-2-one (**85**), which is held in a cisoid arrangement by hydrogen bonding, gives the product **86**, which is stable in anhydrous solvent, but which cyclizes under the influence of water to give methyl 2-methyl-5-oxo-4-(2-oxopropylidene)-2-pyrroline-3-carboxylate (**87**).

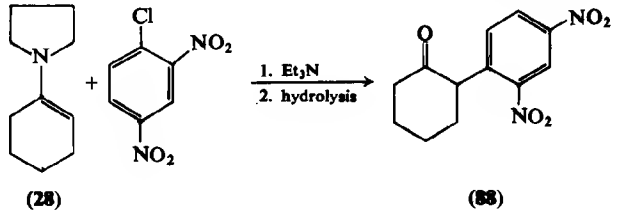


(85) (86) (87)

Enamines have also been shown to react with benzyne (*68*) to give benzocyclobutenes.

D. Arylation

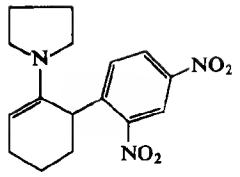
Aryl halides with a halogen activated by electron-withdrawing groups react with pyrrolidine enamines of cyclic ketones (*68*) to give the α-arylated ketones after hydrolysis. The enamine (*28*) with 2,4-dinitrochlorobenzene gave an excellent yield of 2(2,4-dinitrophenyl)cyclohexanone (**88**). The



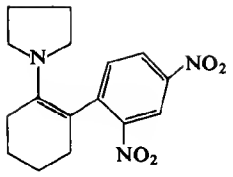
(28) (88)

reaction was shown to go via the enamines **89** and **90** as intermediates, as acylation of the reaction mixture gave both possible acylated ketones on hydrolysis. Reductive cyclization of **88** gave the aminotetrahydrocarbazole (**91**). The pyrrolidine enamine of 2-methylcyclohexanone is arylated in the 6 position.

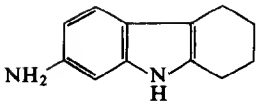
The basicity of the enamine has an overriding influence on the yield of product. Good yields are obtained from the pyrrolidine enamines, poor yields from the piperidine enamines, and the morpholine enamines fail to



(89)



(90)



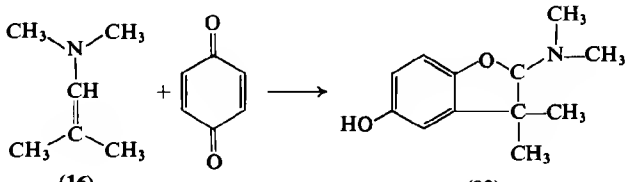
(91)

react. Other activated halides, e.g., 2-chloro-5-nitropyridine, 4-chloro-3-nitropyridine, and 2-chloro-4,5-dicarbethoxypyrimidine have been shown to react equally well (*68*). Similar arylations of heterocyclic enamines, e.g., 1,3,3-trimethyl-2-methylene indoline and 2-benzylidene-3-methylbenzothiazoline (**42**), have been reported (*69,42*).

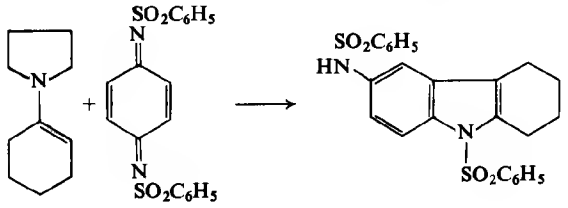
The enamine (**28**) did not undergo C arylation with *p*-nitrochlorobenzene under these conditions, and at higher temperatures N arylation and subsequent cleavage with formation of N-(4-nitrophenyl) pyrrolidine takes place (*68*).

Low yields of C-arylated ketones have also been obtained by reaction of pyrrolidine enamines with diaryl iodonium salts (*68*).

Arylation of enamines with *p*-benzoquinones takes a somewhat different course (*70*). The enamine (**16**) reacts exothermally with *p*-benzoquinone in benzene solution to give 2-(dimethylamino)-2,3-dihydro-3,3-dimethyl-5-benzofuranol (**92**). The reaction of enamines with quinone dibenzenesulfonimide proceeds similarly (*68*). The product from the enamine (**28**) is the tetrahydrocarbazole derivative (**93**).



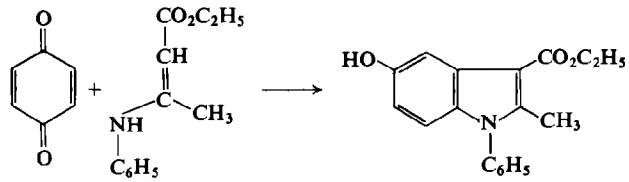
(16) (92)



(28) (93)

Much less work has been done on the arylation of enamino ketones. The enamino ketone (**49**) has been allowed to react with 2,4,6-trinitrochlorobenzene. In this instance the latter reacts as the acid chloride of an acid the anion of which is a good leaving group (*46*). This type of reaction will be discussed in Section IV.A.

Reactions of quinones with enamino ketones have not been reported, but ethyl β-anilinocrotonate (**94**), an enamino ester, has been shown to condense (*71*) with *p*-benzoquinone to give 1-phenyl-2-methyl-3-carbethoxy-5-hydroxyindole (**95**).



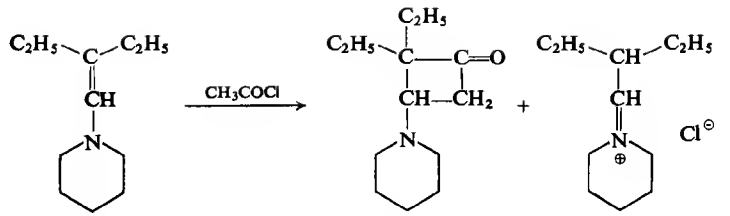
(94) (95)

IV. Acylation

Acylation of enamines can take place on carbon or on nitrogen. In contrast to the N-alkylated products, the N-acylated products either are not stable or are acylating agents so that C acylation is the normal mode of reaction. The enamines are stronger bases than the acylated enamines so that in acylation with acid chlorides half an equivalent of the enamine is lost to the acylation reaction by salt formation. Loss of enamine in this manner can be avoided by the addition of an organic base such as triethylamine (*72*). It has also been shown that the less reactive morpholine enamines give better yields of acylated products (*72*). The acylation of enamines with acid anhydrides or acid chlorides having no α-hydrogen atom appears to be a straightforward reaction at the enamine carbon. The reaction of acid chlorides having an α-hydrogen atom often involves a cycloaddition of the ketene formed by dehydrohalogenation of the acid chloride by the basic enamine. The initial product in these cases is a cyclobutanone derivative which may sometimes be isolated or which subsequently undergoes rearrangement to the normal C-acylated product.

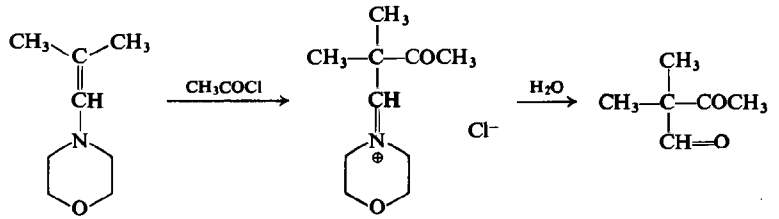
A. Reaction with Carboxylic Acid Chlorides, Anhydrides, and Ketenes

The reaction of the enamine (**96**) with acetyl chloride was reported (*72*) to afford no acyl derivative but the aminocyclobutanone (**97**) and the hydrochloride of the enamine.



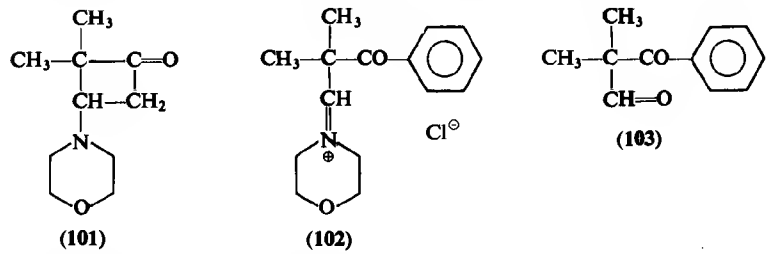
(96) (97)

More recently the acylation of aldehyde enamines has been reinvestigated (*75*) and shown to proceed normally when the enamine is added to the acid chloride. The morpholine enamine of isobutyraldehyde (**98**), on being added to an ether solution of acetyl chloride, afforded the iminium salt (**99**), from which the ketoaldehyde (**100**) was obtained in 66% yield by hydrolysis (*75*).



(98) (99) (100)

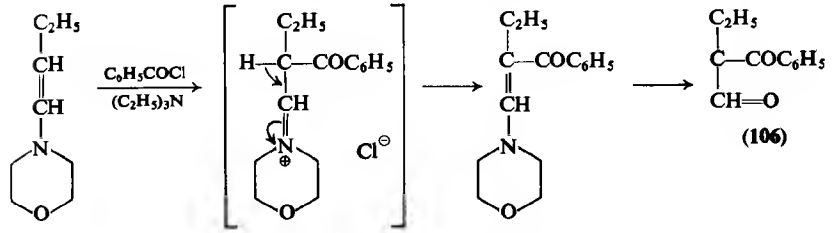
This acylation might still be assumed to proceed via the aminocyclobutanone with subsequent rearrangement, but it was shown (*75*) that the hydrochloride salt of the aminocyclobutanone (**101**), prepared by an alternate method, was not rearranged under the reaction conditions. The intermediacy of (**101**)



(101) (102) (103)

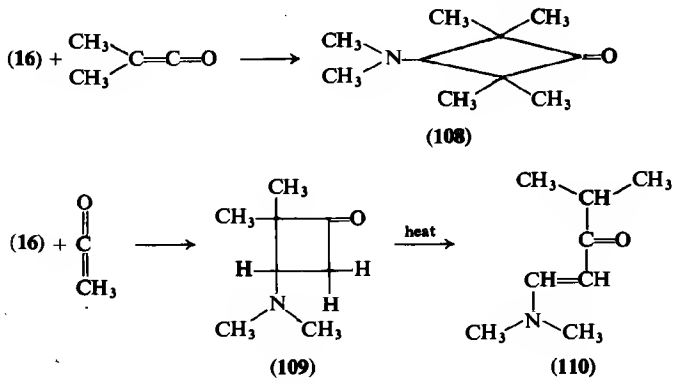
therefore seems unlikely. Under similar reaction conditions in dioxane the enamine (**98**) was acylated by benzoyl chloride to give the iminium salt (**102**) and the ketoaldehyde (**103**) in 86 and 72% yields, respectively. This reaction

was not affected by the addition of base, as the salt (**102**) was isolated even in the presence of triethylamine. When the enamine (**104**) was acylated with benzoyl chloride in the presence of triethylamine, triethylamine hydrochloride was precipitated instead of the iminium salt (**105**). Since hydrolysis of the reaction mixture gave the ketoaldehyde (**106**), it appears reasonable that the salt (**105**) lost the elements of HCl in this case to give the enamino ketone 1-N-morpholino-2-benzoyl-1-butene (**107**).



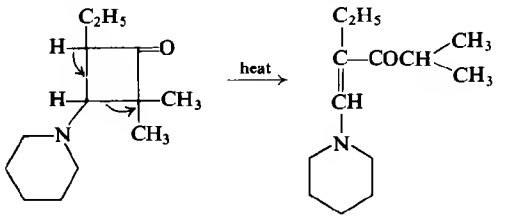
(104) (105) (107) (106)

The reaction of aldehyde enamines with ketenes has been well investigated (*73,74,76–78*) and shown to give cyclobutanone derivatives. The stability of the latter is dependent on the structure of the enamine and the ketene. Thus reaction of the enamine (**16**) with dimethyl ketene gave the thermally stable 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone (**108**). Reaction of **16** with ketene, on the other hand, gives the 3-dimethylamino-2,2-dimethylcyclobutanone (**109**), which on heating rearranges to the enamino ketone (**110**), which is not the product which would be expeeted from acetylation of **16**. An alternate mode of ring opening is shown by the amino cyclobutanone (**111**) derived from reaction of the piperidine enamine of



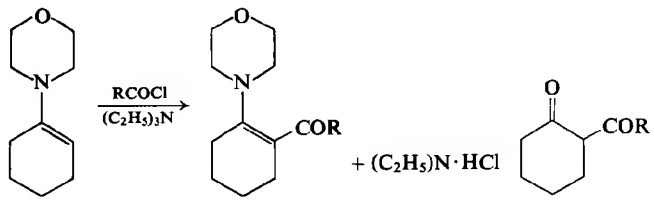
(108) (109) (110)

butyraldehyde and dimethyl ketene. In this case the enamino ketone (**112**) formed is the product which would be expected from acylation of the



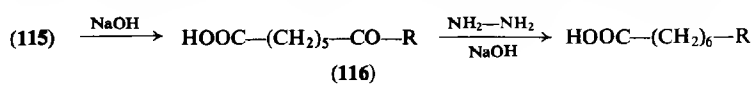
(**111**) (**112**)

enamine with isobutyryl chloride. The enamines derived from cyclic ketones are readily acylated with acyl and aroyl halides (*32,72,79,80–83*). The morpholine enamines give the best yields, and the addition of triethylamine avoids loss of enamine by salt formation. The enamine (**113**) undergoes acylation to give, after acid hydrolysis of the intermediate enamino ketone (**114**), the 1,3-diketone (**115**) in high yield.



(**113**) (**114**) (**115**)

The preparation of long-chain fatty acids has been carried out in this way because cleavage of **115** with strong sodium hydroxide gives the ketoacid (**116**), which is easily reduced by the Wolf–Kishner method to the saturated acid. A similar sequence of reactions can be carried out starting with the cyclopentanone enamine, and this method allows lengthening the chain

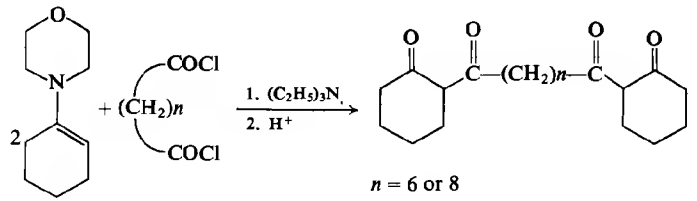


(**116**)

of a carboxylic acid by five or six carbon atoms (*79,81*).

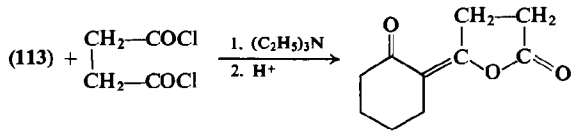
The dicarboxylic acid chlorides from sebacic and azelaic acid react with 2 moles of enamine to give the tetraketone (**117**), which on base cleavage

and reduction gives a dicarboxylic acid with chain length increased by twelve carbon atoms. In this way tuberculostearic acid has been prepared (*83*).



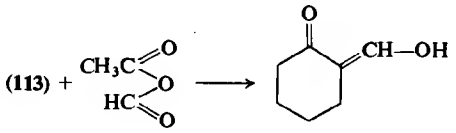
(**113**) (**117**)

Dicarboxylic acid dichlorides with less than seven carbon atoms do not react to give tetraketones similar to **117**, but instead undergo an intramolecular acylation (*72*) to give on hydrolysis the vinylogous acid anhydride (**118**), e.g., from succinyl chloride and the enamine (**113**).



(**118**)

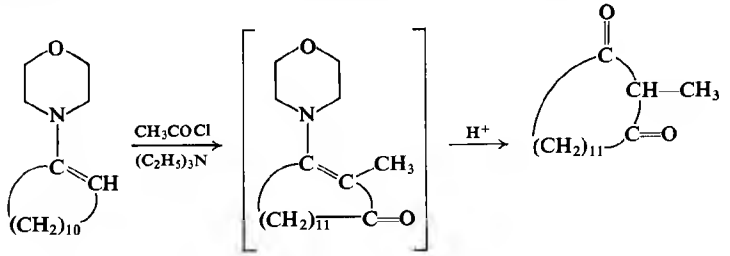
Anhydrides have also been employed (*31*). The mixed anhydride of acetic and formic acid reacts with the enamine (**113**) to give a 50% yield of 2-hydroxymethylene cyclohexanone (**119**).



(**119**)

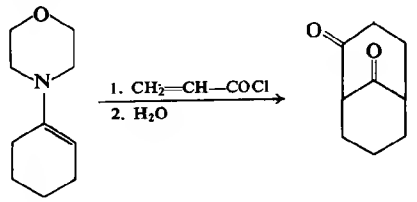
There is some spectral evidence that acylation of enamines of cyclic ketones with acid chlorides having an α-hydrogen in the presence of triethylamine proceeds via the ketene and subsequent cycloaddition (*84*). The intermediate cyclobutanone is then opened to give the enamino ketone which is hydrolyzed to the 2-acyl cyclohexanone. In the case of enamines of larger cyclic ketones the alternate mode of the cyclobutanone opening predominates, with the formation of ring-expanded 1,3-diketones upon

hydrolysis (*85,86*). Thus 1-morpholinocyclododec-1-ene (**120**) on reaction with acetyl chloride in the presence of triethylamine gave an intermediate cyclobutanone which rearranged to the enamino ketone (**121**), which was hydrolyzed by acid to give cyclotetradecan-1,3-dione (**122**).



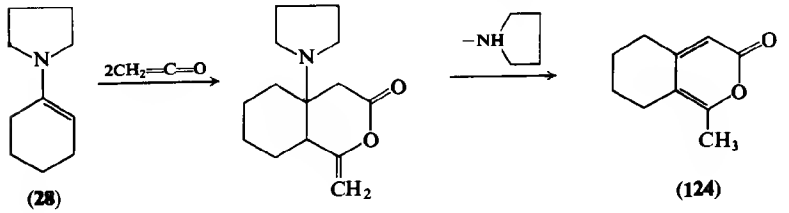
(**120**) (**121**) (**122**)

Acylation of the enamine (**113**) with α,β-unsaturated acid chlorides has been shown (*87*) to give bicyclo(3.3.1)nonan-2,9-diones. Acryloyl chloride on reaction with the enamine (**113**) and subsequent hydrolysis gave bicyclo-(3.3.1)nonan-2,9-dione (**123**). Mechanistic studies suggest that C alkylation by the olefin precedes acylation (*87*).



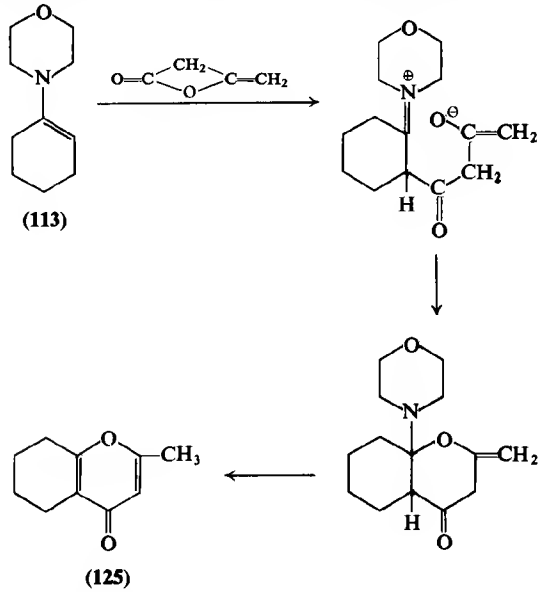
(**113**) (**123**)

The reaction of ketene with the enamine (**113**) is reported (*88*) to give 1-morpholino-2-acetyl-1-cyclohexene i.e., the enamino ketone expected from acylation of (**113**). The pyrrolidine enamine (**28**), however, has been shown to react (*73*) with excess ketene to give the α-pyrone (**124**). On the



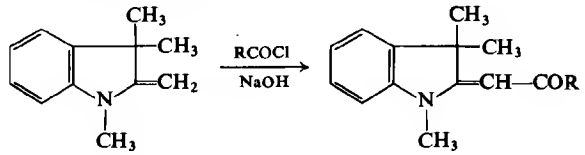
(**28**) (**124**)

other hand, the morpholine enamine (**113**) reacts with excess diketene (*89*) to give the chromone (**125**) and N-acetoacetylmorpholine.

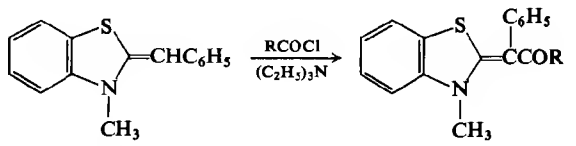


(**113**) (**125**)

Acylation of the heterocyclic enamines e.g., 1,3,3-trimethyl-2-methyl-eneindoline (**126**) and 2-benzylidene-3-methylbenzothiazoline (**42**) takes place normally at the methylene carbon (*42,69*), with both acyl and aroyl chlorides in the presence of base.

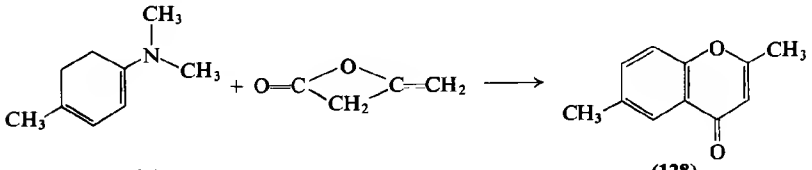


(**126**)



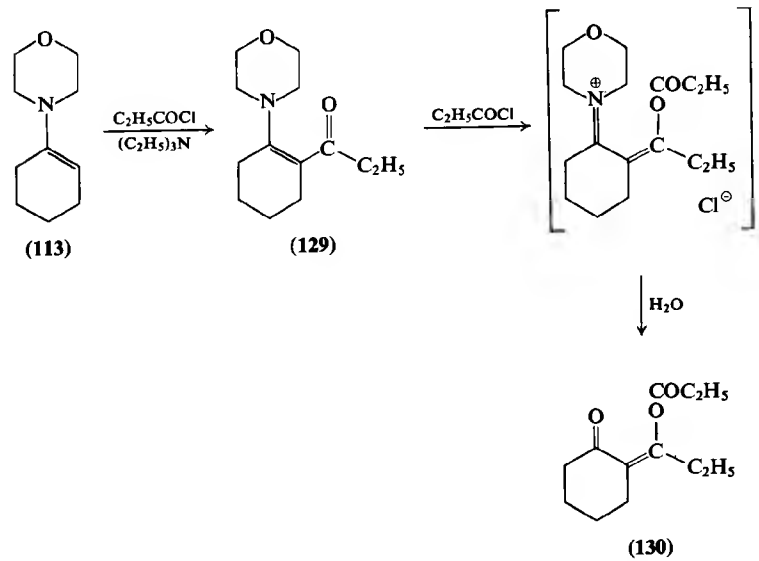
(**42**)

The acylation of dienamines has not been extensively investigated. The dienamine (**127**) prepared by Birch reduction of N,N-dimethyl-*p*-toluidine has been shown to react with diketene (*90*) to give the chromone (**128**), showing that attack occurs at the β-carbon of the dienamine system.



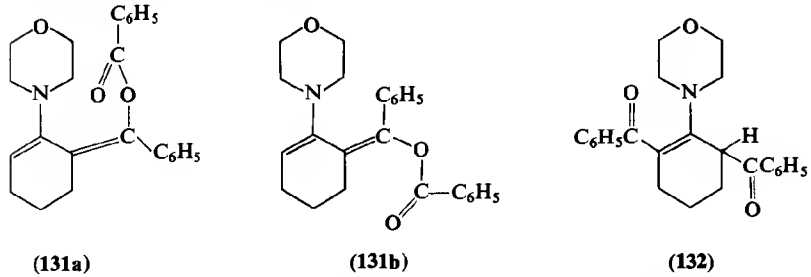
(**127**) (**128**)

The acylation of enamino ketones can take place on oxygen or on carbon. While reaction at nitrogen is a possibility, the N-acylated products are themselves acylating agents, and further reaction normally takes place. The first reported acylation of enamino ketones (*72*) was that of **129**, prepared by acylation of the enamine (**113**), which was shown to have undergone O acylation because on mild hydrolysis the enol ester (**130**) could be isolated. A similar reaction took place with other aliphatic acid chlorides (*80*) and with dibasic acid chlorides [e.g., with succinyl chloride to give **118** above].



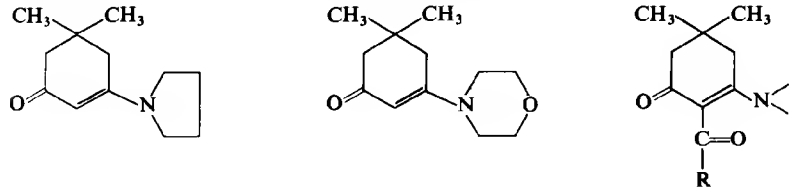
(**113**) (**129**) (**130**)

Acylation with aromatic acid chlorides was believed to occur on carbon (*91*). The dibenzoylation of the enamine (**113**) with benzoyl chloride in the presence of triethylamine has, however, been shown to give a mixture of three products (*92*). The major components are the *cis* and *trans* isomers of the O-acylated enamino ketone (**131a** and **b**) and the minor isomer is the 2,6-diacylated enamine (**132**).



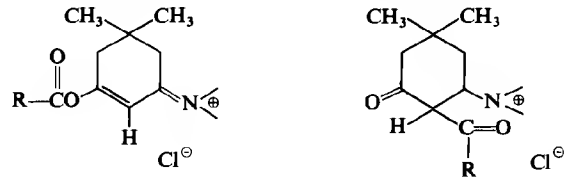
(**131a**) (**131b**) (**132**)

It would thus appear that O acylation is the normal course of the acylation of enamino ketones. Surprisingly the enamino ketones **49** and **50** undergo reaction with acid chlorides not having an α-hydrogen (e.g., benzoyl and pivalyl chlorides) to give the products of C acylation (**133**).



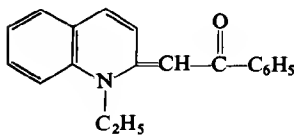
(**49**) (**50**) (**133**)

This result has been rationalized by consideration of the stability of the intermediate iminium salts (*93*). O acylation would give **134**, whereas C acylation would give **135**. The latter can undergo loss of a proton to give the product, whereas **134** cannot, but can revert to reactants, so that in this

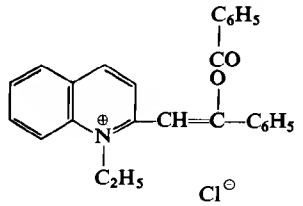


(**134**) (**135**)

case initial O acylation may occur, but the reaction is reversible and does not lead to products. The O-acylated salt can be isolated (*94*). Thus benzoylation of the heterocyclic enamino ketone (**136**) gave the *o*-benzoylated salt (**137**). Further evidence for O acylation is provided by reaction of the

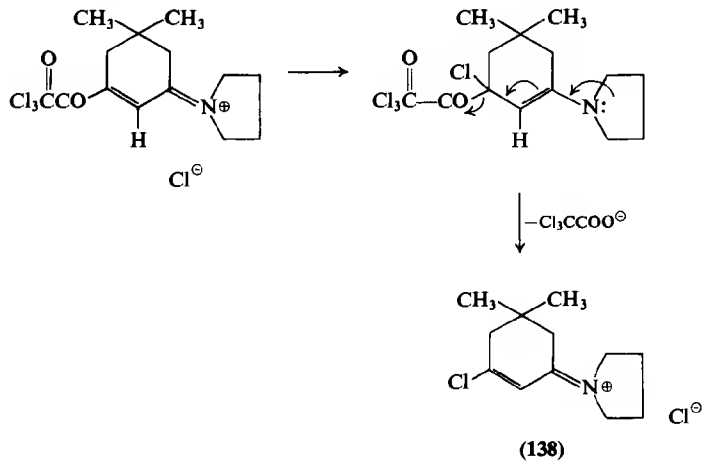


(**136**)



(**137**)

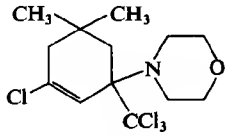
enamino ketone (**49**) with trichloroacetyl chloride (*42*) to give 1-(3-chloro-5,5-dimethyl-2-cyclohexen-1-ylidene)pyrrolidinium chloride (**138**). The latter must have been formed by a reaction sequence involving initial O acylation and subsequent addition of chloride ion to the cation with expulsion of trichloroacetate (i.e., the better leaving group). The salt (**138**) is also formed by reaction of the enamino ketone (**49**) with phosphorus pentachloride (*42*).



(**138**)

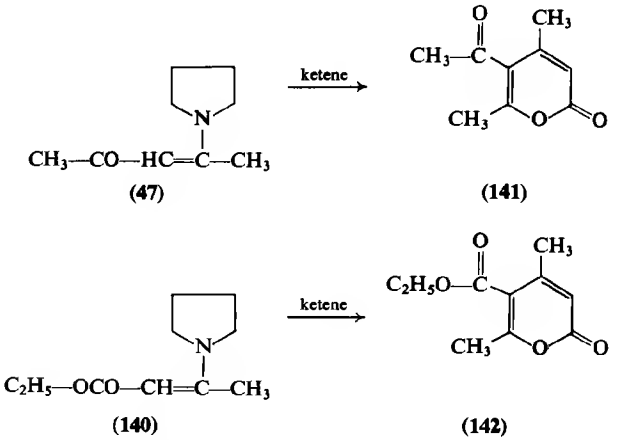
It is of interest to note that 2,4,6-trinitrochlorobenzene reacts similarly with **49** to give the cation of **138** isolated as the perchlorate. In the reaction of the enamino ketone (**50**) with trichloroacetyl chloride (*17*) the chloro-

iminium cation undergoes reaction with trichloromethyl anion (formed by decarboxylation of the expelled trichloroacetate) to give the trichloromethyl derivative (**139**).



(**139**)

The enamino ketone (**49**) reacts with acetyl chloride (*93*) to give the C-acylated product (**133**), whereas the corresponding reaction with the enamino ketone (**50**) gave only the hydrochloride of **50**. As neither **49** nor **50** undergoes reaction with ketene, this suggests that **49**, the enamino ketone derived from pyrrolidine, reacts as an enamine toward acetyl chloride, while **50**, derived from the weaker base morpholine, does not. It is still a strong enough base to remove the elements of hydrochloric acid from acetyl chloride. The enamino ketone (**47**) and the enamino ester (**140**), on the other hand, react with 2 moles of ketene in the manner expected to give the α-pyrone derivatives **141** and **142**, respectively (*73*).

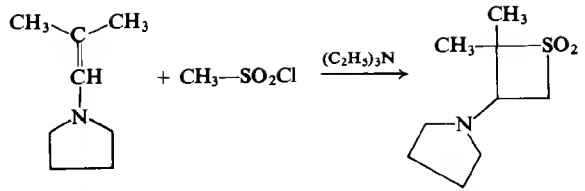


(**47**) (**141**)

(**140**) (**142**)

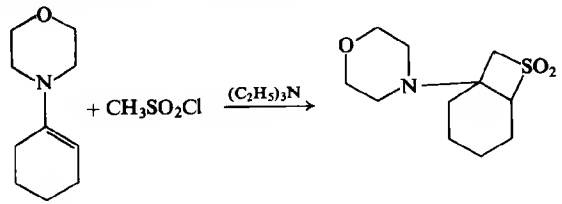
B. Reaction with Sulfonyl Halides

Alkyl sulfonyl chlorides, having an α-hydrogen atom, react with enamines derived from aldehydes and cyclic ketones in the presence of triethylamine to give cyclic sulfones. Thus the enamine (**22**) gave the four-membered cyclic aminosulfone (**143**) on reaction with methanesulfonyl chloride (*95*).



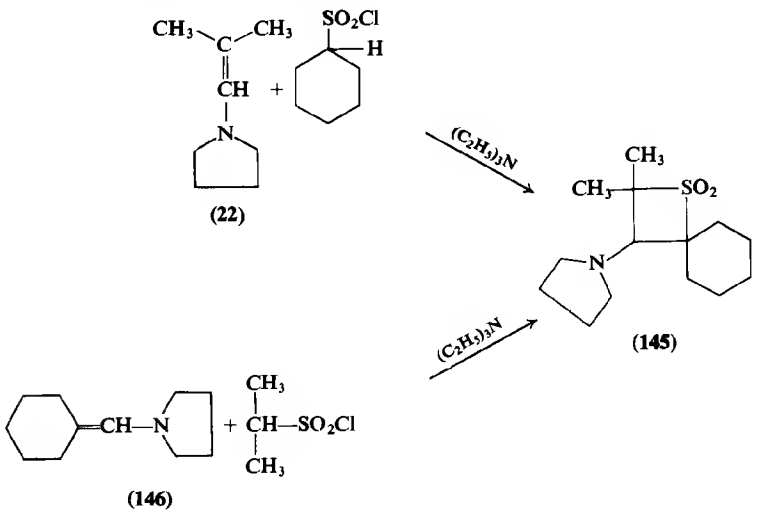
(22) (143)

In a similar manner the enamine (**113**) reacted with methanesulfonyl chloride (*96*) to give the cyclic sulfone (**144**).



(113) (144)

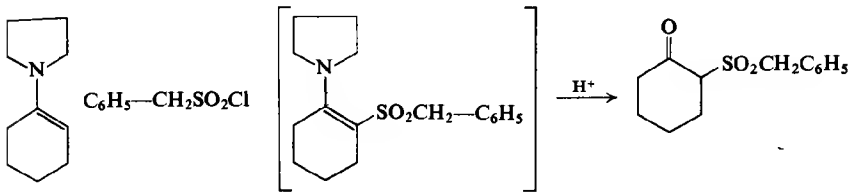
The formation of the same four-membered ring aminosulfone (**145**) from the enamine (**22**) and cyclohexanesulfonyl chloride in 72% yield and from N-(cyclohexylidenemethyl)pyrrolidine (**146**) and 2-propanesulfonyl chloride in 77% yield proves the constitution of these cyclic sulfones (*97*).



(22) (145) (146)

The reaction is postulated as proceeding via dehydrochlorination of the sulfonyl chloride to the sulfene, followed by cycloaddition to the enamine. The possibility that addition of the sulfonyl chloride to the enamine followed by dehydrochlorination, either directly or via the C-sulfonated enamine, results in the formation of the four-membered sulfone has been ruled out (*98–100*).

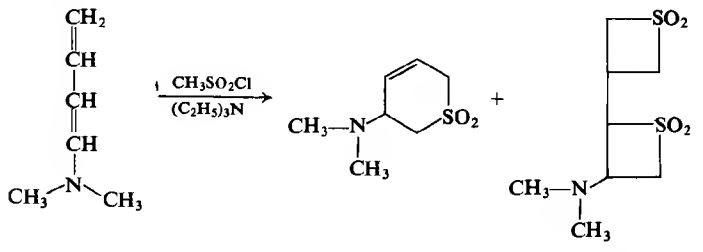
Recently acyclic sulfones have also been isolated (*99,101*). Reaction of the enamine (**28**) with phenylmethane sulfonyl chloride (*101*) gave benzyl-2-oxocyclohexyl sulfone (**147**).



(28) (147)

The formation of acyclic sulfones is favored by increasing substitution at the α-carbon of the sulfonyl chloride and also of the enamine (*97,100*).

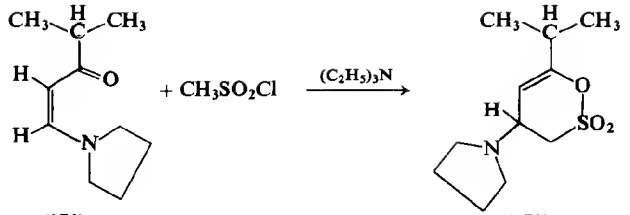
The dienamine (**148**) can react in two ways with methane sulfonyl chloride. In one a 1,4 Diels–Alder-type addition gives **149**; in the other way the initially formed product reacts further to give the bis-cyclic sulfone (**150**) (*102,103*).



(148) (149) (150)

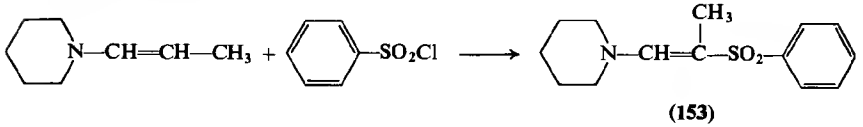
If the cisoid structure of the dienamine is fixed only the Diels–Alder-type addition occurs (*100*).

Methanesulfonyl chloride reacts with enamino ketones (*104*), (e.g., **151**) to give good yields of the enol sulfones (e.g., **152**). The analogy with ketene addition to form α-pyrones (Section IV.A) is obvious.

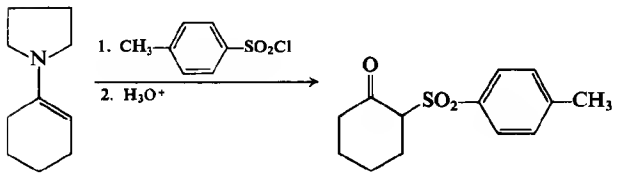


(151) (152)

The aromatic sulfonyl chlorides which have no α-hydrogen and thus cannot form sulfenes give acylic sulfones. Thus 1-piperidinopropene on reaction with benzene sulfonyl chloride (*95*) gave 2-benzenesulfonyl-1-piperidinopropene (**153**). Similarly the enamine (**28**) reacts with *p*-toluenesulfonyl chloride to give the 2-*p*-toluenesulfonylcyclohexanone (**154**) on hydrolysis (*105*).



(153)



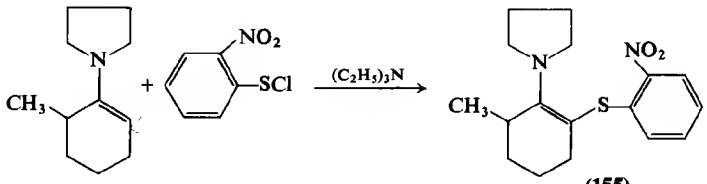
(28) (154)

In the reaction with enamino ketones derived from dimedone (e.g., **49**) *p*-toluenesulfonyl chloride gives the chloroiminium cation (**138**) isolated as the perchlorate. This indicates that initial O sulfonation is followed by addition of chloride ion and subsequent expulsion of tosylate (**42**) in a manner similar to the trichloroacetyl chloride reaction with **49** (Section IV.A).

C. Reaction with Sulfenyl Chlorides

The pyrrolidine enamine of cyclohexanone (**28**) has been shown to react with *o*-, *m*-, and *p*-nitrobenzenesulfenyl chlorides (*105*). A mixture of the 2-mono- and 2,6-bis(*o*-, *m*-, and *p*-nitrophenylsulfenyl)cyclohexanones is obtained on hydrolysis. Only the monosubstituted derivative (**155**) is

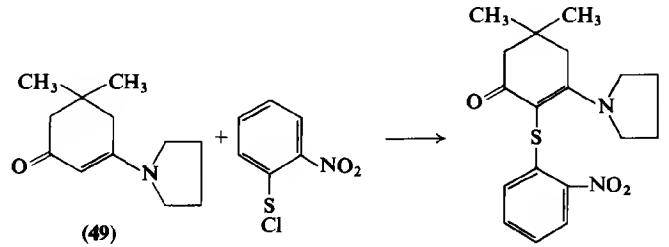
obtained from 6-methyl-1-pyrrolidino cyclohexene and *o*-nitrobenzenesulfenyl chloride.



(155)

An interesting variant of this reaction is the formation of 2-thiaadamantane-4,8-dione by hydrolysis of the reaction product of the bispyrrolidine enamine of bicyclo[3.3.1]nonane-2,6-dione with sulfur dichloride (*106*).

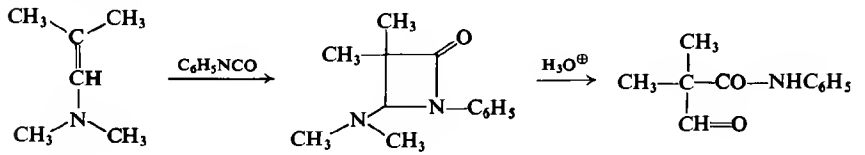
The enamino ketone **49** has also been found to react with *o*-nitrobenzenesulfenyl chloride to give the derivative **156**, having the *o*-nitrophenylthio group substituted in the 2 position (*93*), i.e., the same position at which normal acylation with acid chlorides takes place.



(49) (156)

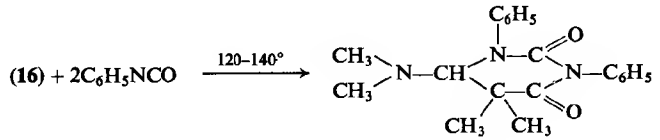
D. Reaction with Isocyanates and Isothiocyanates

The reaction of isocyanates with enamines disubstituted at the β-carbon gives β-amino-β-lactams (*107,108*). Thus the enamine (**16**) reacted exothermally with phenylisocyanate to give (*33*) dimethyl-1-phenyl-4-dimethylamino-2-acetidinone (**157**), which was converted by acid hydrolysis to 2-formyl-2-methyl propionanilide (**158**).



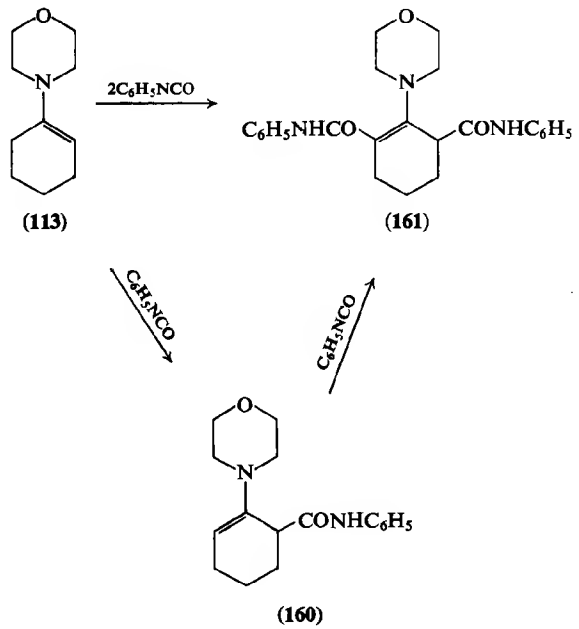
(16) (157) (158)

When the reaction is carried out at 120–140°, 2 moles of phenyl isocyanate react with one of the enamine (**16**) to give 1,3-diphenyl-5,5-dimethyl-6-dimethylamino hydrouracil (**159**) (*109*).



(**159**)

Enamines of cyclic ketones do not form cycloaddition products, but give the mono- or dicarboxanilides (*110,111*). Thus the enamine (**113**) on reaction with 1 equivalent of phenyl isocyanate gave **160**. Treatment of **113** with 2 equivalents, or **160** with 1 equivalent, of phenyl isocyanate gave the 2,6-disubstituted product (**161**). Mild acid hydrolysis of **160** and **161** produced the corresponding cyclohexanone(2-mono- and 2,5-di)carboxanilides (*110*).



(**113**) (**161**) (**160**)

Proof that the second mole of phenyl isocyanate did not react at the nitrogen of **160** was provided by the reaction of the enamine from 2-methylcyclohexanone, which gave only the monocarboxanilide on reaction with excess phenyl isocyanate.

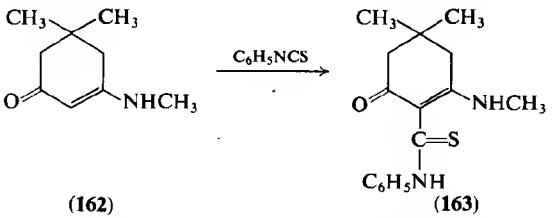
The difunctionality of the enamines of cyclic ketones toward phenyl isocyanate provides the ideal situation for a potential polymer. The properties of the polyamides produced by addition of various diisocyanates to the enamines of cyclic ketones have been reported (*111a*).

The reaction of the enamines of cyclic ketones with alkyl isocyanates, acyl isocyanates, phenyl isothiocyanates, and acyl isothiocyanates has also been reported (*112*). The products are the corresponding carboxamides. The products from the isothiocyanates have been utilized as intermediates in the preparation of various heterocyclic compounds (*113*).

The rate of addition of isocyanates to enamines increases with decreasing basicity of the isocyanate nitrogen and with increasing basicity of the enamine nitrogen (*112*).

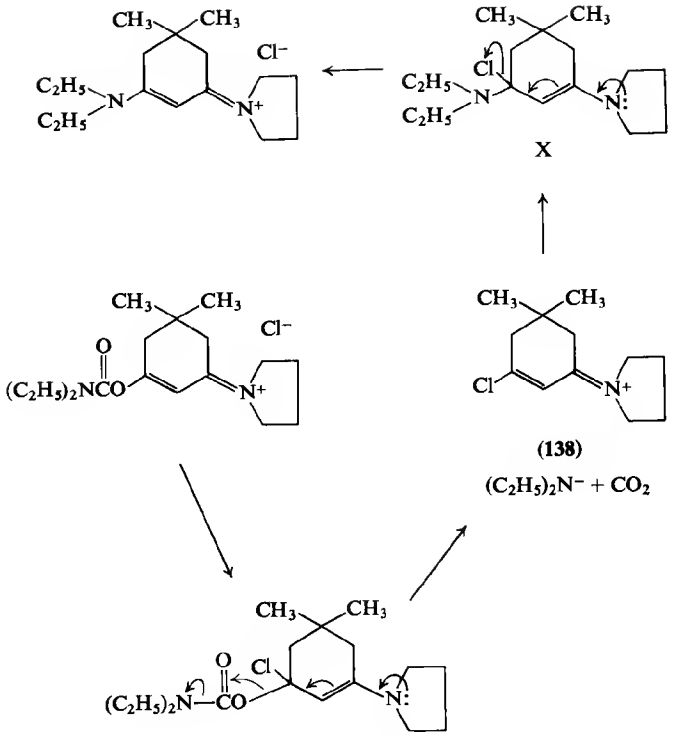
The reaction of the enamines **28** and **113** with N,N-dimethyl carbamoyl chloride has been reported to give no isolable β-keto amides (*63*).

The reaction of enamino ketones with isocyanates and isothiocyanates has not been studied extensively. The enamino ketone (**162**) has been shown to react with phenyl isothiocyanate to give **163**, the product of C acylation (*114*). Enamino ester derivatives of acetoacetic ester react similarly with isothiocyanates, also giving the C-acylated products (*115*).



(**162**) (**163**)

The enamino ketone (**49**) was reported to give no identifiable products on reaction with N,N-dimethyl carbamoyl chloride (*63*). However, reaction of (**49**) with N,N-diethyl carbamoyl chloride in refluxing chlorobenzene gave the N-(3-diethyl-amino-5,5-dimethylcyclohex-2-en-1-ylidene)pyrrolidinium salt, isolated as the perchlorate. The latter must have been formed as outlined in Scheme I, involving initial O carbamoylation followed by an addition–elimination reaction to give **138** cation which can react with diethylamino anion by a further addition–elimination displacement to give the product (*46*).



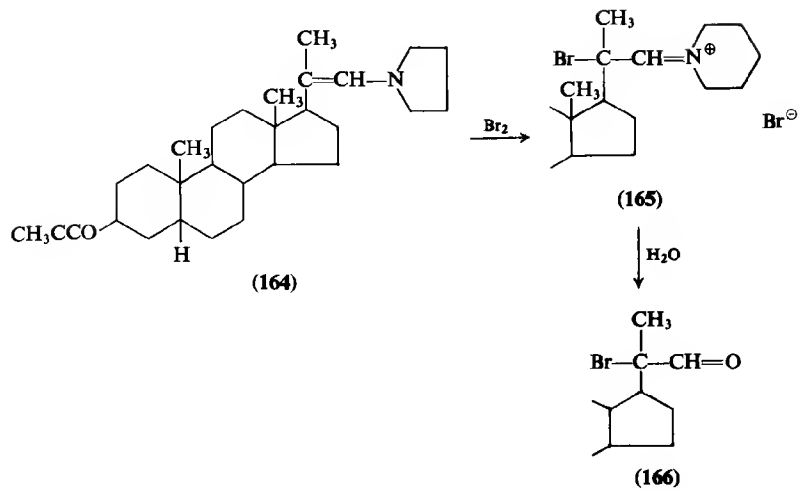
Scheme 1

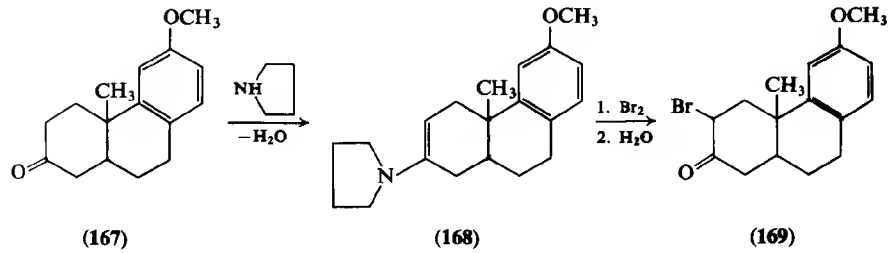
V. Reaction with Miscellaneous Electrophiles

A. Halogenation

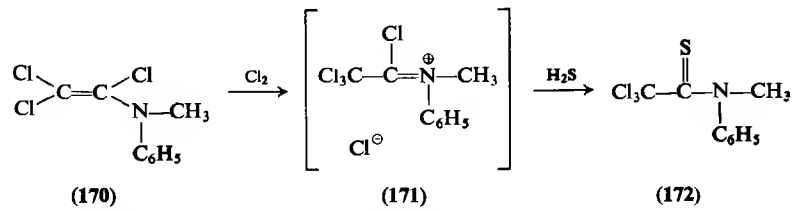
The halogenation of enamines is formally analogous to protonation with salt formation. Thus the steroidal enamine (**164**) undergoes bromination (*116*) to give the β-bromo iminium bromide (**165**), which is readily hydrolyzed to the β-bromo aldehyde (**166**).

This method of bromination has been employed in the selective bromination (*117*) of the ketone (**167**). While direct bromination results in bromination not only in the position alpha to the ketone but also in the aromatic ring, bromination of the enamine (**168**) and subsequent hydrolysis gave only the monobrominated product (**169**).

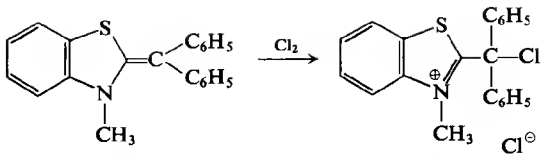




Chlorination of enamines has also been reported (*42,118*). Thus the trichlorovinylamine (**170**) has been chlorinated to **171**, which was not isolated but treated with hydrogen sulfide to give the thioamide (**172**) (*118*).



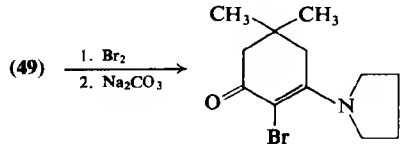
A stable chloroiminium chloride (**173**) has been isolated from the chlorination of the heterocyclic enamine (**174**) (*42*).



(174) (173)

Stable β-chloro and bromo enamines have recently been obtained by reaction of enamines with the corresponding N-halosuccinimides (*118a*).

Enamines from steroidal ketones have been fluorinated by means of perchloryl fluoride (*119,120*) to give the α-fluorinated ketones. The enamino ketone (**49**) was brominated to give a salt from which the bromoenamino ketone (**175**) was isolated on treatment with dilute carbonate solution (*121*).

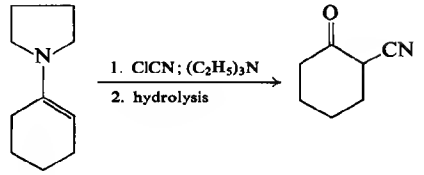


(175)

Recently α-chloro-β-chlorocarbonyl enamines have been obtained from ynamines and phosgene (*121a*).

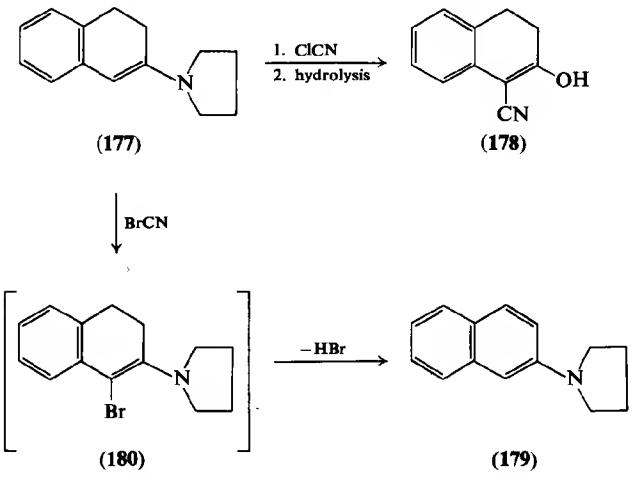
B. Reaction with Cyanogen Halides

The pyrrolidine enamines of the cyclic ketones cyclopentanone through cyclononanone have been reacted with cyanogen chloride to give high yields of the corresponding α-cyanoketones on hydrolysis (*122*). Thus the enamine (**28**) on reaction with 1 equivalent of cyanogen chloride in the presence of 1 equivalent of triethylamine in dioxane gave a 60% yield of 2-cyanocyclohexanone (**176**) on hydrolysis. The corresponding piperidine and morpholine enamines are less satisfactory in this reaction and gave yields of only 19 and 6% of **176**, respectively. The pyrrolidine enamine of 2-methylcyclohexanone and 2-phenylcyclohexanone gave 2-cyano-6-methylcyclohexanone and 2-cyano-6-phenylcyclohexanone in 66 and 77% yields, respectively. Only in the 2-methylcyclohexanone case was a small amount of 2-cyano-2-methylcyclohexanone observed (*122*).



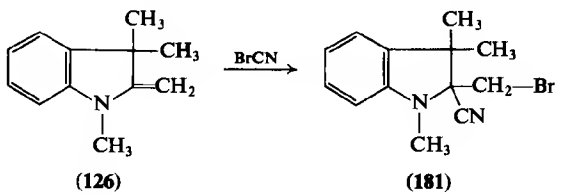
(28) (176)

The pyrrolidine enamine of 2-tetralone (**177**) was converted to 1-cyano-2-tetralone, which exists almost entirely in the enolic form (**178**), by reaction with cyanogen chloride (*123*). Reaction of **177** with cyanogen bromide gave N-naphthylpyrrolidine (**179**), presumably via the unstable bromoenamine (**180**). The latter observation is in accord with the mode of reaction of the heterocyclic enamine (**126**) with cyanogen bromide, which resulted in the



(177) (178) (180) (179)

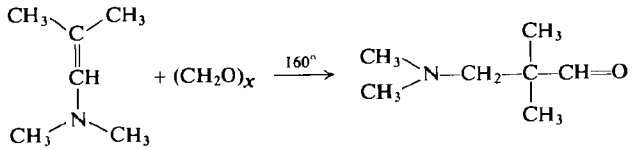
formation of **181** (*124*). These observations are also in agreement with the opposite polarization of cyanogen bromide and chloride (*125*).



(126) (181)

C. Reaction with Aldehydes

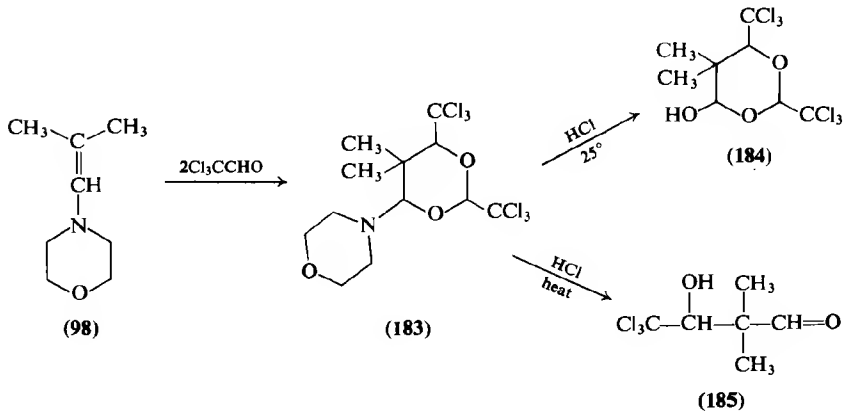
The reaction of the dimethylamine or piperidine enamine of isobutyraldehyde with paraformaldehyde gives the substituted aminopivalaldehydes (*127*), which have also been obtained by the Mannich reaction of isobutyraldehyde, formaldehyde, and the corresponding amine (*127*). Thus the enamine (**16**) gave β-dimethylaminopivalaldehyde (**182**). A mechanistic study using formaldehyde-d_2 showed that this is a simple variation of the



(16) (182)

Mannich reaction as a part of the enamine (**16**) is hydrolyzed into its components by the residual water in the paraformaldehyde (*126*).

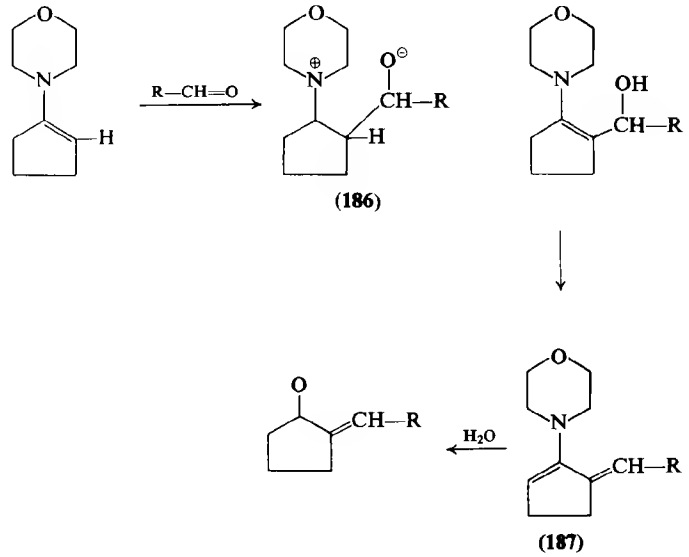
When chloral was used as the aldehyde 2 equivalents reacted with 1 equivalent of the enamine (**98**) regardless of the ratio of reactants or order of addition to give 2,6-bis(trichloromethyl)-5,5-dimethyl-4-morpholino-*m*-dioxane (**183**) in 83% yield (*126*). Hydrolysis of **183** with hydrochloric acid at room temperature gave the hemiacetal (**184**), but when heated with acid, the aldol product (**185**) was formed.



(98) (183) (184) (185)

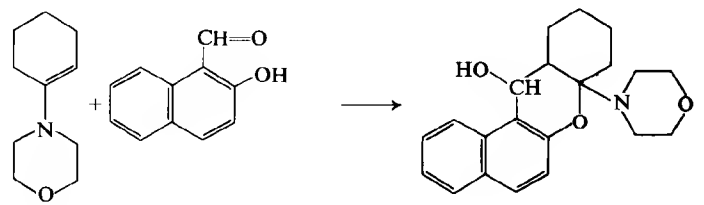
The enamines of cyclic ketones, on reaction with aliphatic and aromatic aldehydes, give good yields of the 2-monoalkylidene derivative of the corresponding ketones (*128*). The first step in the reaction appears to be the

formation of the dipolar species **186**, which can undergo proton transfer and elimination of water to give **187**, which on hydrolysis gives the 2-alkylidene cyclanone.

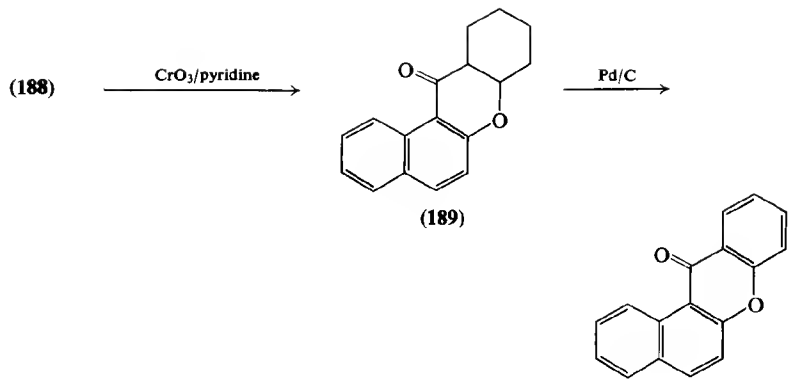


(186) (187)

The intermediacy of dipolar species such as **186** has been demonstrated by reaction of enamines with 2-hydroxy-1-aldehydes of the aromatic series (*129*). The enamine (**113**) reacts in benzene solution at room temperature with 2-hydroxy-1-naphthaldehyde to give the crystalline adduct (**188**) in 91% yield. Oxidation with chromium trioxide–pyridine of **188** gave **189** with β elimination of the morpholine moiety. Palladium on charcoal dehydrogenation of **189** gave the known 1,2-benzoxanthone (*129*).

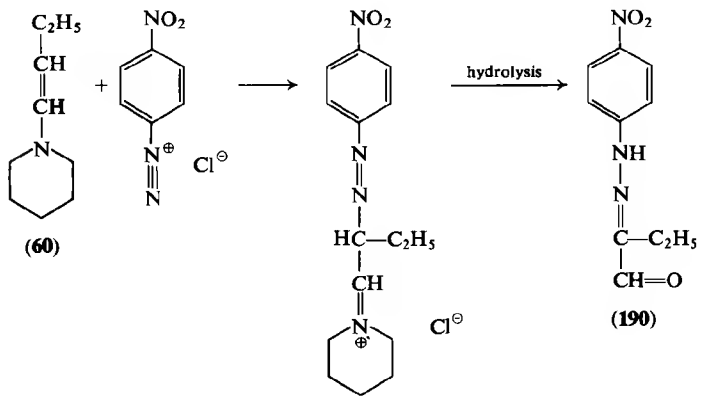


(113) (188)

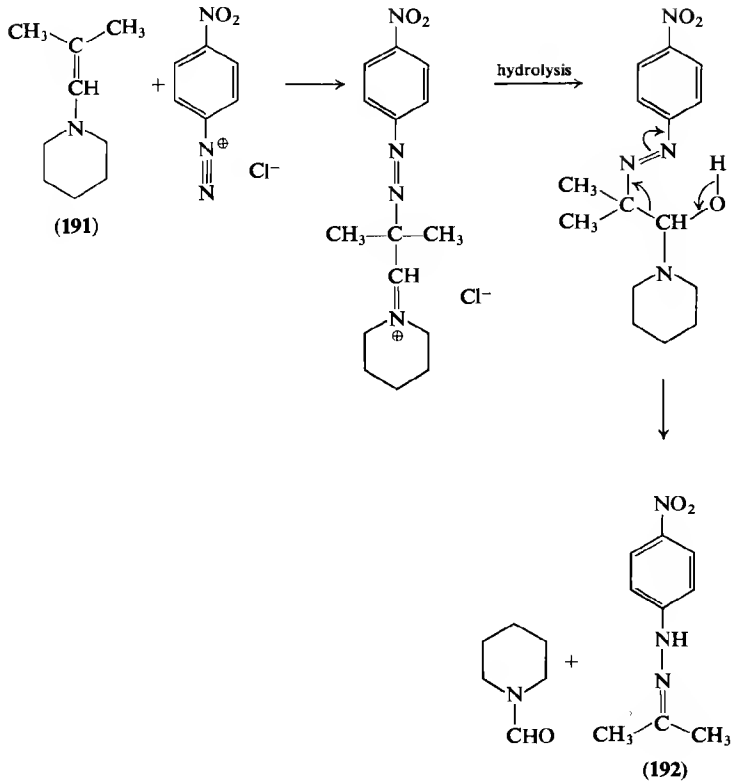


D. Reaction with Aromatic Diazonium Salts

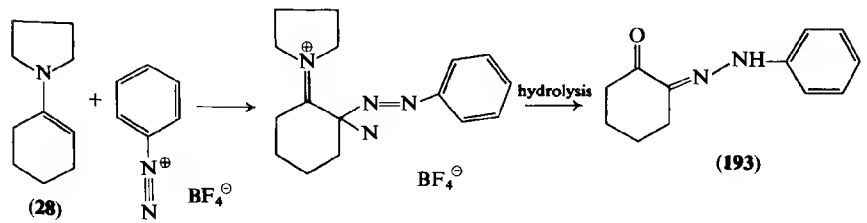
Aldehyde enamines react with aromatic diazonium salts in two ways, depending on the degree of substitution at the enamine carbon (*130*). Thus the piperidine enamine of butyraldehyde (**60**) reacted with *p*-nitrophenyldiazonium chloride to give the *p*-nitrophenylhydrazone of the α-keto aldehyde (**190**).



The enamine (**191**) from isobutyraldehyde on treatment with *p*-nitrophenyldiazonium chloride, on the other hand, gave the *p*-nitrophenylhydrazone of acetone (**192**) and presumably N-formyl piperidine, although the latter was not isolated.



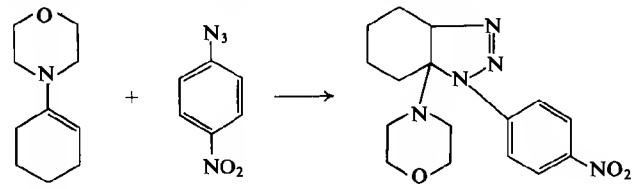
Enamines of cyclic ketones react similarly (*68,131*). Thus the enamine (**28**) gave a good yield of the monophenylhydrazone of 1,2-cyclohexanedione (**193**) on reaction with phenyldiazonium fluoborate and subsequent hydrolysis (*68*). The products (**193**) have been cyclized to the corresponding



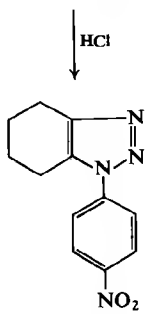
indoles (*131*). In contrast the heterocyclic enamine 1,3,3-trimethyl-2-methyleneindoline (**126**) gave an azo compound (*132*).

E. Reaction with Aromatic Azides

Enamines from cyclic ketones give derivatives of triazole (*133,134*). The enamine (**113**) reacts with *p*-nitrophenyl azide to give the triazoline (**194**), which on treatment with acid gives the triazole (**195**).



(113) (194)



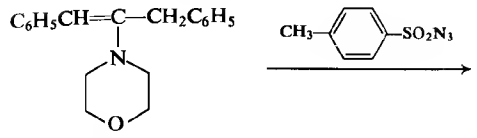
(195)

Tosyl azide reacts differently to give sulfonamide derivatives (*134*). The morpholine enamine from dibenzylketone (**196**) for instance reacted with tosylazide to give **197** and phenyldiazomethane (**198**), which was trapped with acetic acid giving benzyl acetate (*134*).

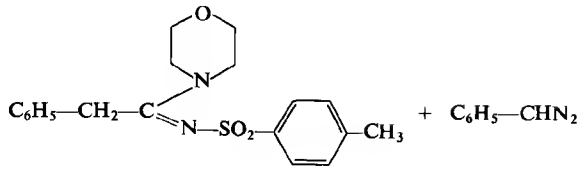
Hydrazoic acid has been shown to add to dienamines to give a complex mixture of 1-azido- and 1,3-diazido-amines (*135*).

F. Reaction with Ethyl Azodicarboxylate

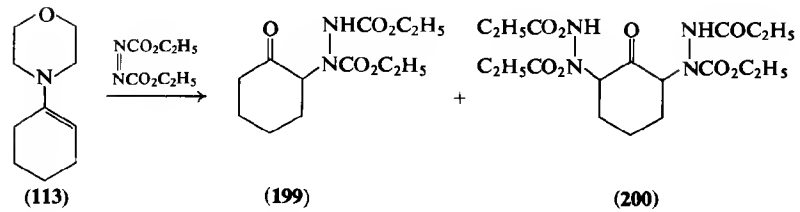
The reaction of morpholine enamines of cyclic ketones with ethyl azodicarboxylate has also been demonstrated (*56,136*). The enamine (**113**) on reaction with ethyl azodicarboxylate can give the 2- or 2,6-bis(N,N′ dicarboxyhydrazino)cyclohexanones **199** and **200**, respectively, on hydrolysis.



(196)



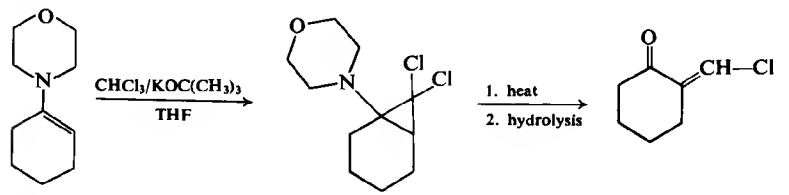
(197) (198)



(113) (199) (200)

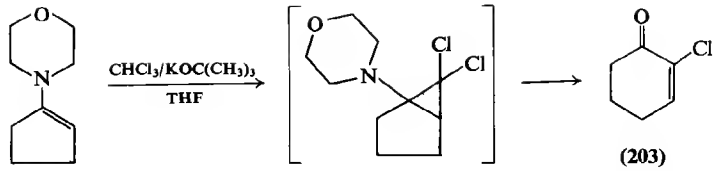
G. Reaction with Dichlorocarbene

The reaction of enamines derived from cyclohexanone with dichlorocarbene to give the 1:1 adducts is now well established (*137–139*). The morpholine enamine (**113**) reacted with dichlorocarbene at −10 to −20° in tetrahydrofuran to give the stable crystalline adduct (**201**). Thermal decomposition followed by an aqueous work-up gave an α,β-unsaturated ketone identified as 2-chloromethylene-cyclohexan-1-one (**202**) (*139*).



(113) (201) (202)

Reaction of the morpholine or piperidine enamine of cyclopentanone, however, gives an unstable adduct which rearranges under the reaction conditions and an aqueous work-up to give the ring expanded ketone 2-chloro-2-cyclohexen-1-one (**203**) (*138,139*).

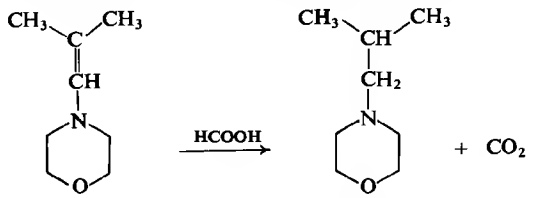


(203)

A similar difference in behavior of the dichlorocarbene adducts of cyclohexene and cyclopentene has been noted previously (*140*).

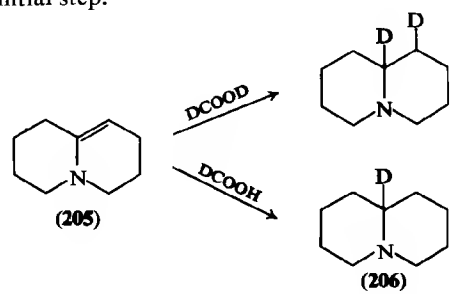
H. Reaction with Formic and Trichloroacetic Acids

Enamines derived from aldehydes have been treated with formic acid under the conditions of the Leuckart–Wallach reaction (*141*) to give saturated tertiary amines (*142*). The enamine (**98**) reacts vigorously with formic acid at room temperature to give N-isobutyl morpholine (**204**).



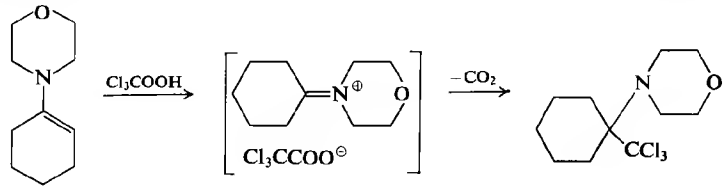
(98) (204)

The reaction has been applied to more complex enamines (*13*) and to dienamines (*19*). The reduction may be rationalized by initial protonation at the enamine carbon and subsequent decarboxylation of formate ion and addition of the hydride ion to the iminium cation. This mechanism has been given support by the reaction of the enamine (**205**) with deuterated formic acid (*143*) to give the corresponding amines. The formation of **206** on reaction with DCOOH clearly indicates that protonation at the enamine carbon is the initial step.



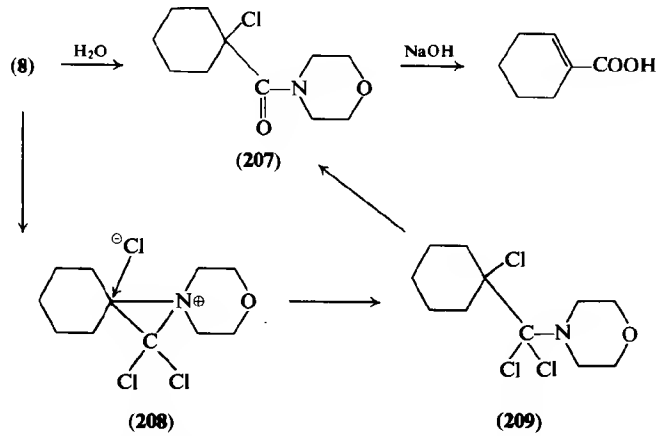
(205) (206)

Trichloroacetic acid behaves somewhat similarly in that protonation of the enamine occurs (*17,17a*). Subsequent decarboxylation of the trichloroacetate gives trichloromethyl anion, which adds to the iminium cation to give the trichloromethyl amine derivative. Thus the enamine (**113**) undergoes reaction with trichloroacetic acid to give N-[1-(trichloromethyl)cyclohexyl]-morpholine (**8**). The latter compound undergoes rearrangement on



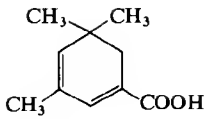
(113) (8)

heating with aqueous solvents to give the α-chloroamide (**207**), which can be converted to 1-cyclohexene-1-carboxylic acid on vigorous basic hydrolysis (*17*).



The conversion of **8** to **207** probably proceeds via the aziridinium salt **208**, which can suffer opening (*144*) to **209**. The latter is readily hydrolyzed to the amide (**207**).

A similar sequence of reactions has been shown to take place with the dienamine derived from isophorone and morpholine (*17*). Reaction of this enamine with trichloroacetic acid gave a trichloromethyl derivative which was not isolated but which undergoes rearrangement and hydrolysis with base to give the diene acid (**210**).



(210)

I. Reaction with Diborane and Aluminum Hydrides

The reduction of the double bond of an enamine is normally carried out either by catalytic hydrogenation (*145*) or by reduction with formic acid (see Section V.H) or sodium borohydride (*146,147*), both of which involve initial protonation to form the iminium ion followed by hydride addition. Lithium aluminum hydride reduces iminium salts (see Chapter 5), but it does not react with free enamines except when unusual enamines are involved (*148*).

However, diborane and certain aluminum hydrides such as mixed hydride reagents lithium aluminum hydride and aluminum chloride are electrophilic in nature and can add directly to enamines. The reaction involves the addition of the alumino cation and a hydride ion to the α and β positions, respectively, of the enamine. This adduct can have then either the aluminum functional group replaced by a hydrogen during hydrolysis to form the saturated amine (*149*) or the aluminum and amine functional groups eliminated to form the corresponding unsaturated compound (*150,151*). The net effect of the first pathway is hydrogenation of the enamine, while that of the second pathway is hydrogenolysis of the enamine. Of the three mixed hydride reagents, $AlCl_2H$, $AlClH_2$, and AlH_3, the proportion of the olefin was greatest with AlH_3 and least with $AlCl_2H$ (*150*). Hydrogenolysis of enamines also takes place when they are treated with diisobutyl aluminum hydride (*152*).

Diborane adds to enamines with the hydride ion going to the α position and the borane group to the β position, except when steric conditions around the β carbon prohibit it (*150*). Treatment of this intermediate with refluxing acetic acid produces the saturated amine (*146*) or the aminoborinic acid (*153*). When the intermediate is refluxed with acetic or propionic acids in diglyme, the corresponding alkenes are obtained in good yields through the hydrogenolysis reaction (*153*).

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5

NUCLEOPHILIC ADDITION TO IMINIUM SALTS

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I. Introduction

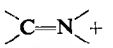
In most reviews of enamine chemistry the reactions of iminium salts are scattered throughout the review and are consequently not covered in a comprehensive manner. This chapter will be an attempt to look at reactions that, at one stage or another, proceed by nucleophilic addition to the iminium intermediate. The subject of enamines has been reviewed (*1–4*) and certain aspects of iminium salt chemistry such as reduction of aromatic quaternary salts have been treated in detail (*5*). Consequently, the reduction of aromatic quaternary salts with complex hydrides will be presented here only briefly. Although the literature (especially 1950–1967) has been checked with care, the author can make no claim to completeness. The

occasional inclusion of iminium salt reactions in papers otherwise concerned only with enamines makes exhaustive literature search virtually impossible.

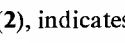
II. Structure, Preparation, and Detection of Iminium Salts

A. Structure of Iminium Salts

The positively charged carbon–nitrogen double bond

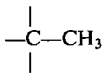


has been often compared to carbonyl compounds to explain the reactivity of iminium salts. Just as the carbonyl can be thought of as a resonance hybrid of two forms, the iminium salts can be thought of as a resonance hybrid of two similar charged forms shown (**1**). The

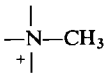
distance, 1.30 Å, determined by X-ray crystallography for N,N-dimethylisopropylideneiminium perchlorate (**2**), indicates that the  bond is

(**1**)

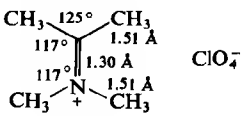
very short. The molecule has some interesting features such as equal bond lengths (1.51 Å) for



and



and equal angles (125°) for $CH_3—C—CH_3$ and $CH_3—N_+—CH_3$ (*6*).

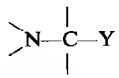


(**2**)

Self-consistent molecular orbital calculations (SCMO) have been performed on the π system using both molecular self-consistent field (SCF) and variable electronegativity method (VESCF). There was observed a large variation in bond orders and charges depending on the method of calculation and choice of parameters. The π-bond orders varied from 0.8312 to 0.9951, while the charge on carbon varied from 0.5560 to 0.0989 as the method of calculation was changed (SCMO, VESCF) or the integrals were changed (theoretical to Pariser and Parr). While the calculations are not conclusive, they do indicate a considerable amount of charge on carbon that accounts for the observed reactivity of the iminium salts and justifies the frequent comparison to carbonyl systems (*6*).

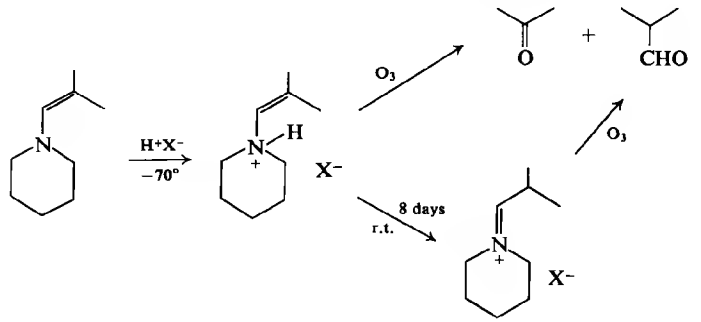
B. Preparation of Iminium Salts

Iminium salts can be made in a number of ways such as protonation of enamines (*7*), alkylation of aldimines and ketimines (*8,9*), cleavage of a covalent bond in a



system (*8,10*), or by direct combination of aldehydes and ketones with amine salts (*11–15*). We shall examine all of the common methods in more detail.

Iminium salts are readily available from C protonation of the corresponding enamines (*7*). Experimentally the procedure is very simple: The enamine dissolved in ether or some other solvent is treated with an appropriate acid such as anhydrous hydrogen chloride or 70% perchloric acid. The iminium salt usually separates and is then collected. Protonation at low temperatures



(**3**)

provides evidence that N protonation occurs first, followed by rearrangement to a C-protonated iminium salt (*16*). The evidence for N protonation of a variety of enamines at −70° comes from reaction of ozone, diazomethane, or lithium aluminum hydride (LAH) with N-protonated salts. Freshly prepared N-isobutylidenepiperidinium hexachlorostannate (**3**) gives a mixture of isobutyraldehyde and acetone after ozonolysis and reductive isolation. If the salt is allowed to stand for 8 days prior to ozonolysis, only isobutyraldehyde is obtained (*16*).

TABLE 1

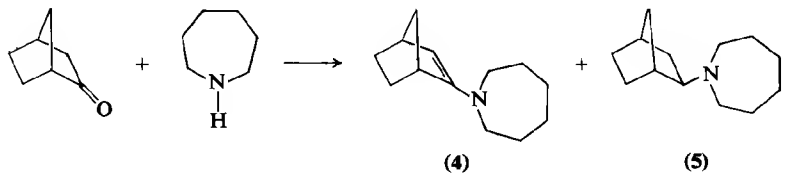
Compound	Time at room temperature	Diazomethane per cent protonation At C	Diazomethane per cent protonation At N	$LiAlH_4$ per cent protonation At C	$LiAlH_4$ per cent protonation At N
1-N-Morpholylbutene	0	16	74	10	80
	60 min	93	0	83	0
1-N-Pyrrolidylisobutene	0	2	80	5	83
	48 hr	90	0	91	0
1-N-Morpholylisobutene	0	0	82	2	84
	48 hr	83	5	92	0
1-N-Pyrrolidylcyclohexene	0	93	2	91	0
	24 hr	95	0	—	—
1-N-Piperidylcyclohexene	0	12	81	25	68
	24 hr	89	8	87	7
1-N-Morpholycyclohexene	0	11	86	18	76
	19 hr	81	10	93	2

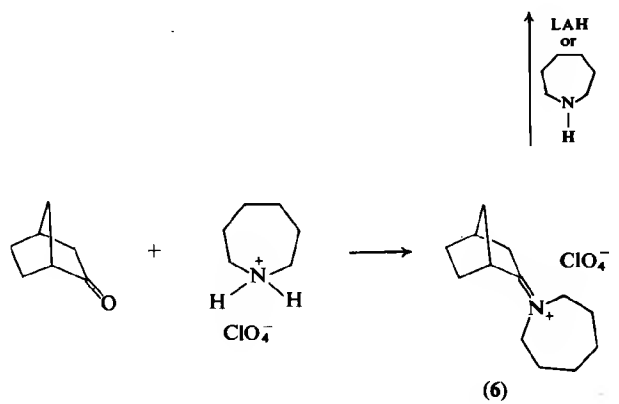
In a similar manner N-(2-ethyl)butylidenepiperidinium hexachlorostannate gives mostly diethyl ketone and only a little of 2-ethylbutanal when a fresh solution is ozonized. If allowed to stand for a period of time, the only product obtained by ozonolysis is 2-ethylbutanal (*16*).

The determination of position of protonation by reaction with diazomethane was performed as follows: The enamine was treated at −70° with ethereal hydrogen chloride and the suspension of precipitated salt was treated with diazomethane and allowed to warm slowly to −40°, at which temperature nitrogen was liberated. The reaction with lithium aluminum hydride (LAH) was carried out similarly except that an ether solution of LAH was added in place of diazomethane. The results from reaction of diazomethane and LAH (*16*) are summarized in Table 1.

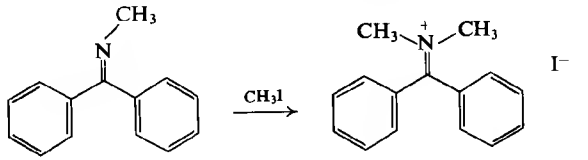
The close agreement of the three methods supports the contention that protonation at low temperatures first occurs at nitrogen and is followed by a proton shift to give the iminium salt (*16*). The rate of this rearrangement is dependent on temperature, the nature of the amine, and the nature of the carbonyl compound from which the enamine was made. Even with this complication the availability of iminium salts is not impaired since the protonation reaction is usually carried out at higher temperatures than −70°. Structurally complicated enamines such as trichlorovinyl amine can be readily protonated (*17,18*).

Another type of complication has been shown to exist (*19,20*) in the reaction of norcamphor and hexamethyleneimine. In addition to the expected 2-N-hexamethyleneiminobicyclo[2.2.1]-2-heptene (**4**) there was obtained a second major component which was eventually identified as 2-N-hexamethyleneiminobicyclo[2.2.1]heptane (**5**). The perchlorate salt of **5** was thought to be nortricyclenamine (*19*) because of its properties. Preparation of N-2-bicyclo[2.2.1]heptylidenehexamethyleneiminium perchlorate (**6**), the expected product from protonation of **4**, and reduction of **6** with LAH gave **5**. The reduction of **4** to **5** by excess hexamethyleneimine must be regarded as highly unusual.

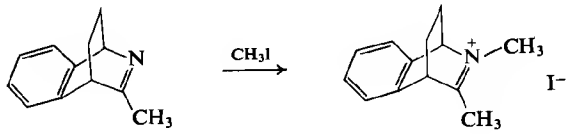




The alkylation of aldimines and ketimines as a method for obtaining iminium salts is now useful only for the preparation of iminium salts not accessible by any of the newer methods. The preparation of **7** and **8** illustrates the conversion of ketimines to iminium salts (*9,21*).

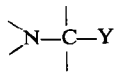


(7)

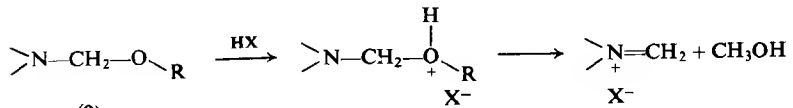


(8)

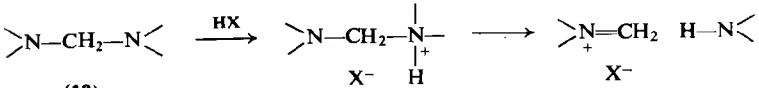
The cleavage of a



bond can result in the formation of iminium salts (*4,8,22,23*). The general reaction is that of an acid with an appropriately substituted tertiary amine. The reaction of α-aminoethers (**9**) and methylene diamines (**10**) proceeds by protonation and elimination of an alcohol or amine (*22,23*). Depending on the nature of the anion, the iminium salt can be isolated or used directly.

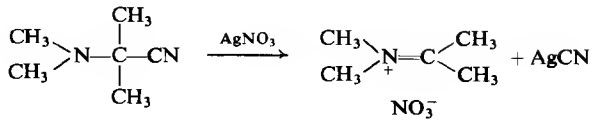


(9)



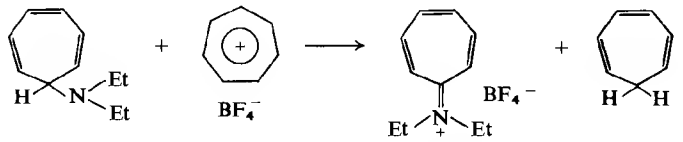
(10)

It is possible to prepare iminium salts from aminonitriles such as **11** and silver nitrate (*10*). The reported yields (20–60%) are not particularly high, but the method was useful in the preparation of simple iminium salts such as isopropylidinedimethylaminium nitrate (**12**) (*10*).

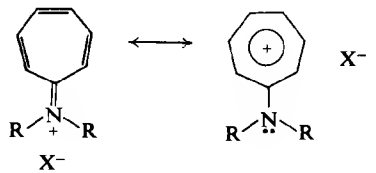


(11) (12)

The cleavage of a carbon–hydrogen bond (hydride abstraction) has been reported for 7-alkylaminocycloheptatrienes to yield tropenylideniminium salts (*10a,10b*). This unique class of compounds had been prepared

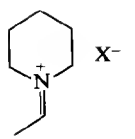


once before by another route, but not examined in detail (*10c*). The hydride abstraction reaction appears to be general since a wide variety of tropenylideniminium salts have been prepared (*10a,10b*). The relative importance of the two resonance forms that can be written for tropenylideniminium

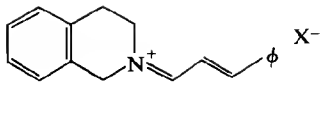


salts when determined will merit attention. Another iminium salt with possible nonbenzenoid aromatic character is 1,2-diphenyl-3-dimethylaminocyclopropenyl fluoroborate, which has been synthesized by treating ethoxydiphenylcyclopropenyl fluoroborate with dimethylamine (*10d*). It possesses the unusual property of remaining undecomposed upon recrystallization from hot water.

The initial investigation of the reaction of aldehydes and ketones with complex secondary amine salts was that of Lamchen et al. (*11*). A few salts had been observed before by Zincke and Würker (*24*), but the reaction was not examined in detail. Lamchen et al. prepared a number of compounds that were presumed to be iminium salts. The amine salts were halostannates, halobismuthates, haloantimonates, and hexahaloplatinates. Among the reported products were N-ethylidenepiperidinium (**13**) and N-cinnamilidenetetrahydroisoquinolinium (**14**) salts.

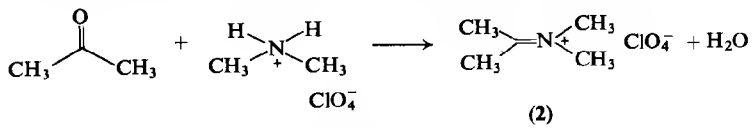


(13)



(14)

A recent adaptation of the procedure employing perchlorate and fluoroborate salts has been reported by Leonard and Paukstelis (*15*). This report includes proof of structure by direct comparison to iminium salts prepared by protonation of enamines. The general reaction reported was that of a ketone or aldehyde with a secondary amine perchlorate to give iminium salts. A large structural variety of carbonyl compounds and several amine



(2)

salts were tested and all gave the expected iminium products. Several iminium salts for which no route through an enamine was possible were formed from aldehydes such as benzaldehyde and pyrrolidinium perchlorate. The combination of amine salts with aldehydes or ketones seems to be very well suited for preparation of large quantities of pure iminium salts. Salts with simple anions such as chloride, bromide, nitrate, and sulfate which were investigated were far inferior to perchlorate or fluoroborate salts in the preparation of iminium salts (*15*).

C. Detection of Iminium Salts

The presence of iminium salts can be detected by chemical means or by spectroscopic methods. The chemical means of detecting iminium salts are reactions with nucleophiles and are the subject of this review. The spectroscopic methods are more useful for rapid identification because with the large number of model compounds available now the spectroscopic methods are fast and reliable. The two methods that are used primarily are infrared and nuclear magnetic resonance spectroscopy. Some attempts have been made to determine the presence of iminium salts by ultraviolet spectroscopy, but these are not definitive as yet (*14,25*).

The first correlation for the determination of enamines and iminium salts was that of Leonard and Gash (*7*), who prepared a series of enamines and the corresponding iminium salts and compared the infrared spectra. There was observed a shift of 20–50 cm^{-1} toward higher frequencies whenever an

enamine was converted to its iminium salt. A recent examination (*25*) has found at least two exceptions, but confirmed the previous observations in most respects. The observed infrared maxima for enamines and the corresponding iminium perchlorates are given in Table 2 (*7,27–29*).

A careful analysis of the variation of infrared maximum with structure seems to indicate a number of features that affect the position of the maximum. In the bicyclic series it is obvious that the change in the maximum is very dependent on the ring size in which the enamine double bond is located. Whenever the enamine double bond is exocyclic to a five-membered ring, the enamine maximum is 1666 cm^{-1} or higher and averages about $1680 \pm 10\ cm^{-1}$. If the enamine double bond is exocyclic to a six- or higher-membered ring, the maximum is about 1650 cm^{-1}. If, in addition to being exocyclic to a six-membered ring, the enamine double bond is also endocyclic to a five-membered ring, then the enamine frequency is even lower (approximately 1630 cm^{-1}). The structure of the iminium salts in the series that Reinecke and Kray (*26*) examined were very similar—they had a tetrasubstituted double bond endocyclic to a five- or six-membered ring. The variation of the iminium maximum was much smaller ($1686 \pm 10\ cm^{-1}$). The enamines of cyclic ketones had maxima in the range 1650–1625 cm^{-1}, depending on ring size, and the pyrrolidinium salts of the cyclic ketones (*28*) had maxima of 1705, 1665, 1655, and 1649 cm^{-1} for cyclopentylidene-, cyclohexylidene-, cycloheptylidene-, and cyclooctylidenepyrrolidinium perchlorates, respectively. The methylene cycloalkanes follow this same type of trend, decreasing frequency with increasing ring size (*30*). Superimposed on the ring size trends are the shifts in frequency associated with change in the extent of substitution of a double bond. These factors easily suffice to understand systems where the iminium salt has the lower frequency than the enamine.

Nuclear magnetic resonance has revolutionized structure determination of iminium salts. A compilation of various resonances for acyclic and cyclic iminium salts are given in Tables 3 and 4 for comparison purposes and for determination of trends. It should be noted that the simplest symmetrically substituted iminium salt (**2**) has its resonance for $\overset{+}{N}—CH_3$ at $\tau = 6.46$ and for

$$\diagdown N^{+}{=}C—CH_3$$

at $\tau = 7.53$ with a coupling constant between the two of 2.1 Hz (*15*). In ring systems the methylene hydrogens adjacent to

$$C{=}N\diagup^{+}$$

TABLE 2

Infrared Frequencies of Enamines and Iminium Salts

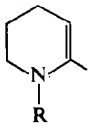
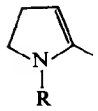
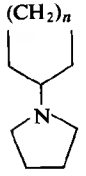
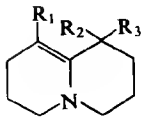
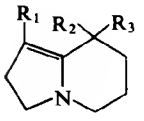
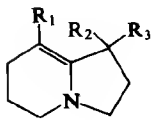
Structure	R	Enamine film, ν_{max}, cm^{-1}	Iminium salt nujol, ν_{max}, cm^{-1}		Ref.
	CH_3^-	1650	1686	+36	7
	$CH_3CH_2CH_2CH_2^-$	1649	1684	+35	7
	CH_3^-	1639	1685	+46	7
	$CH_3CH_2CH_2CH_2^-$	1665	1686	+21	7
	n				
	2	1630	1705	+75	28
	3	1638	1665	+27	28
	4	1629	1655	+26	28
	5	1625	1649	+24	28
	R_1 R_2 R_3				
	H H H	1653	1696	+43	26
	CH_3^- H H	1648	1678	+30	26
	H CH_3 CH_3^-	1631	1676	+45	26
	ϕ^- H H	1629	1685	+56	26
	H H H	1676 (1647sh)	1692	+16	26
	CH_3^- H H	1689	1685	−4	26
	H CH_3^- H	1672	1695	+23	26
	H CH_3^- CH_3^-	1666	1691	+25	26
	CH_3 CH_3^- H	1690	1680	−10	26
	H H $CH_3CH_2^-$	1678	1695	+17	26

TABLE 3

NMR Correlations for Iminium Salts (28)

Chemical shift of various groups in:

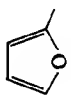
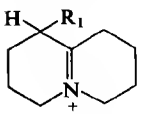
Structure	R_1	R_2	+N—CH_2^-	+N=C(H)	+N=C(CH_3)	+N=C(CH_2^-)
	CH_3^-	CH_3^-	6.03m	—	7.48(J = 1.4)	
	CH_3^-	$CH_2CH_3^-$	6.00m	—	7.53(J = 1.3)	7.23(J = 8.0)
	Et^-	Et^-	5.95m	—	—	7.22(J = 8.0)
	—$(CH_2)_5$—		6.03m	—	—	7.22m
	ϕ—	CH_3^-	5.73m	—	7.21	—
			6.10m			
	ϕ—	H	5.80bm	1.01(J = 2.1)	—	—
	ϕCH=CH—	CH_3^-	5.95m	—	7.43	—
	H	—$CH(CH_3)_2$	5.74m	1.66(J = 9.0)	—	—
			5.95m	(J = 2.0)		
	H	—$CH(Et)_2$	5.66m	1.58(J = 10.0)	—	—
			5.87m	(J = 1.9)		
	H	H	5.75	1.22	—	—
	ϕCH=CH—	H	5.92	1.32(J = 10.0)	—	—
				(J = 1.8)		
	—$C(CH_3)_3$	H	5.82	1.73(J = 2.1)	—	—
	—CH_3		6.00	—	8.0	—

TABLE 4

NMR Correlations for Bicyclic Iminium Salts

Structure		+ N—CH_2		+ N=C^{CH_2}		Ref.
		5-ring	6-ring	5-ring	6-ring	
	R_1					
	H	—	6.29	—	7.23	*7*
	H	—	6.30	—	7.25	*26*
	CH_3	—	6.20	—	7.19	*26*

R_1	R_2	R_3	R_4					
H	H	H	H	5.85	6.30	6.80	7.21	*26*
CH_3	H	H	H	5.79	6.29	6.82	7.25	*26*
H	H	CH_3	H	5.88	6.29	6.7	7.26	*26*
H	H	CH_3	CH_3	5.70	6.06	—	7.10	*26*
CH_3	CH_3	H	H	5.77	6.24	6.80	—	*26*
CH_3	H	CH_3	H	5.88	6.25	6.6	7.1	*26*
H	H	Et	H	5.86	6.24	6.7	7.28	*26*
H	H	H	ϕ	5.54	6.01	—	7.31	*26*

occur about 0.3–0.4 ppm lower field in five-membered rings than in six membered rings.

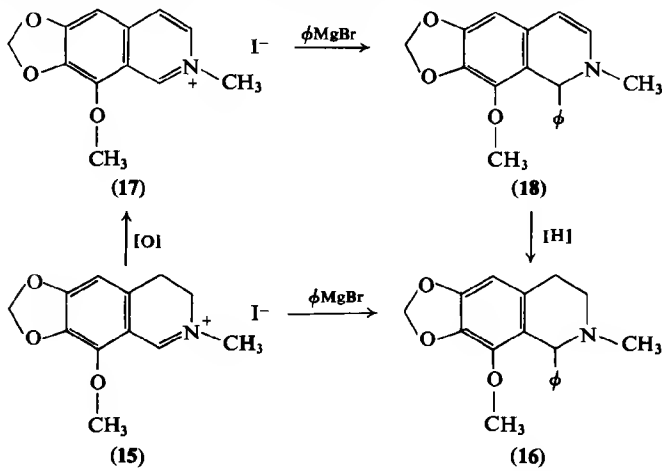
III. Addition of Nucleophiles to Stable Imlnium Salts

A. Addition of Organometallic Reagents

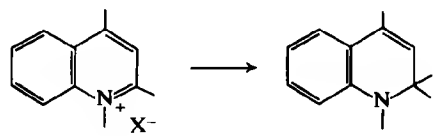
Organometallic reagents react with iminium salts to give C-alkylated products. The reactions can be divided into two categories: the reactions of pyridinium, quinolinium, and isoquinolinium salts; and the reactions of

simple iminium salts. Most of the observations have been made with Grignard reagents, but from the examples available it appears that lithium reagents react in the same way.

A review of the literature prior to 1953 on reactions of pyridinium, quinolinium, and isoquinolinium salts is available (*31*). The reactions will be described here only briefly. The initial observation was that of Freund et al. (*32–37*), who found that treatment of various derivatives of hydrastinine (**15**) with Grignard reagents yielded addition products, such as **16**.



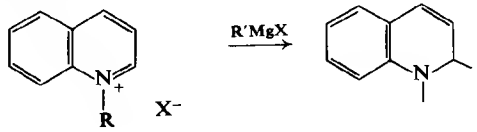
Oxidation of **15** to **17** followed by reaction with phenylmagnesium bromide and reduction gave **16**, indicating that the isoquinolinium salt (**17**) reacted with the Grignard reagent at the same position. Another example of addition to quinolinium salts is that of Craig (*38*), who found that treatment of 2,4-dimethylquinolinium methiodide (**19**) with methyl magnesium iodide gave a C-alkylated product whose structure was shown to be **20**.



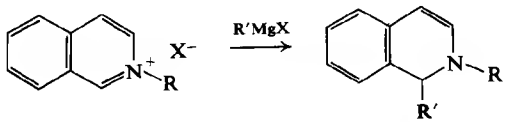
(**19**) (**20**)

Since the initial discovery there have been several investigations that have examined the Grignard reaction with quinolinium and isoquinolinium salts

(*39,41*). In general, quinolinium salts (**21**) give products from addition at the 2 position (**22**) and isoquinolinium salts (**23**) give products from addition at the 1 position (**24**).



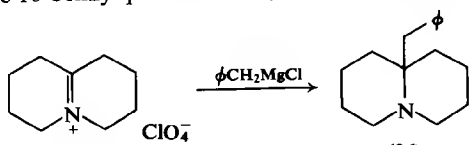
(**21**) (**22**)



(**23**) (**24**)

The reaction of quinolinium and isoquinolinium salts with dialkyl cadmium has been observed to be slow and occurs in relatively poor yield. The structures of the products are the same as those obtained from reactior with Grignard reagents and the yields ranged from 0–20% (*40*). Leadin references to other observed reactions of quinolinium and isoquinolinium salts with Grignard reagents can be found in the above cited review (*31*).

Simple iminium salts react with organometallic reagents in an analogous way to yield addition products (*9,42–48*). The results of many such addition reactions are listed in Table 5. The yields of addition compounds are good, generally in the range of 60–80%. A typical example is the reaction of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (**25**) with benzyl magnesium chloride to give 10-benzylquinolizidine (**26**) in 68% yield (*48*).



(**25**) (**26**)

There are several reports that alkylated pyridine N-oxides react with Grignard reagents to give 2-alkylated pyridines (*50,51*).

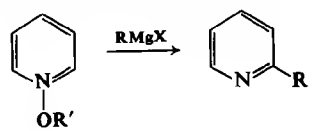
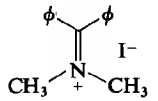
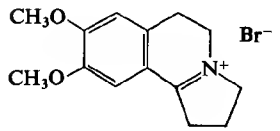
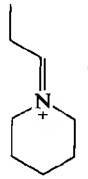
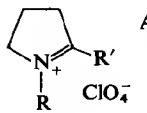
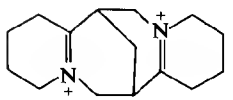
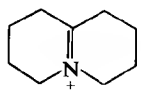
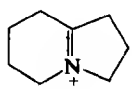


TABLE 5

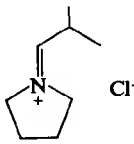
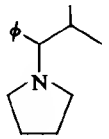
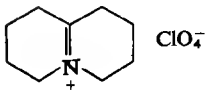
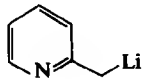
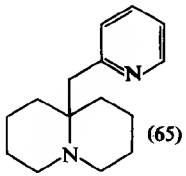
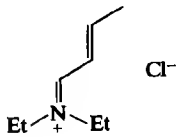
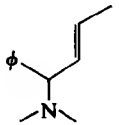
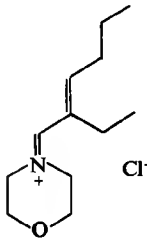
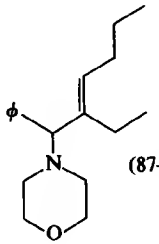
Reaction of Grignard Reagents with Iminium Salts

Compound	Grignard reagent	Ref.
	φCH₂MgCl CH₃MgI	*49* *44, 9*
	—CH₂MgBr	*45*
	CH₃MgI φCH₂MgCl (82)	*16*
 All combinations of R, R'=CH₃, Et, *n*-Pr, *n*-Bu	CH₃MgI EtMgBr PrMgBr BuMgBr	*43*
	MeMgI EtMgBr	*46*
	MeMgI EtMgI (71) φCH₂MgCl (68)	*47*
	MeMgI	*48*

The number of examples of reaction with alkyllithium reagents is very limited (*14,48*). The similarity of the reaction to Grignard addition suggests that similar products will be obtained. This suggestion is supported by the examples shown in Table 6.

TABLE 6

Reaction of Iminium Salts with Lithium Reagents

Compound	Reagent	Product (yield)	Ref.
	ϕ-Li	 (70)	*14*
		 (65)	*48*
	ϕ-Li	 (13)	*14*
	ϕ-Li	 (87–97)	*14*

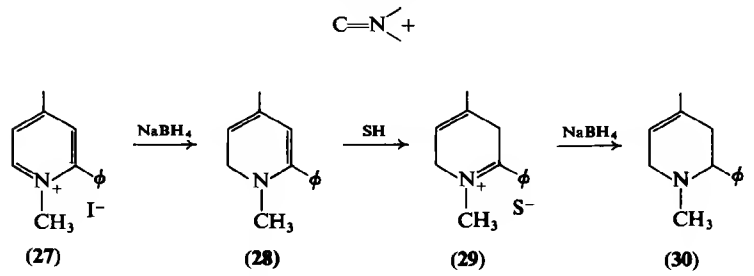
It should be noted that the products from addition to conjugated iminium salts occur primarily by 1,2-and not 1,4-addition (*14*).

In some cases Grignard reagents cause reduction of the iminium salt to the corresponding saturated amine (*51a*).

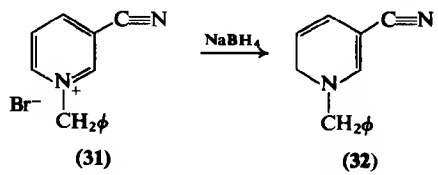
B. Addition of Hydride

The reduction of iminium salts can be achieved by a variety of methods. Some of the methods have been studied primarily on quaternary salts of aromatic bases, but the results can be extrapolated to simple iminium salts in most cases. The reagents available for reduction of iminium salts are: sodium amalgam (*52*), sodium hydrosulfite (*53*), potassium borohydride (*54,55*), sodium borohydride (*56,57*), lithium aluminum hydride (*58*), formic acid (*59–63*), H_2, and platinum oxide (*47*). The scope and mechanism of reduction of nitrogen heterocycles with complex metal hydrides has been recently reviewed (*5,64*), and will be presented here only briefly.

When a pyridinium salt such as (**27**) is treated with sodium borohydride, the final product is the tetrahydropyridine (**30**). The mechanism for this reaction was proposed by Katritzky (*65*) and experimentally verified by Anderson and Lyle (*66–68*). The sequence is visualized as reduction of the

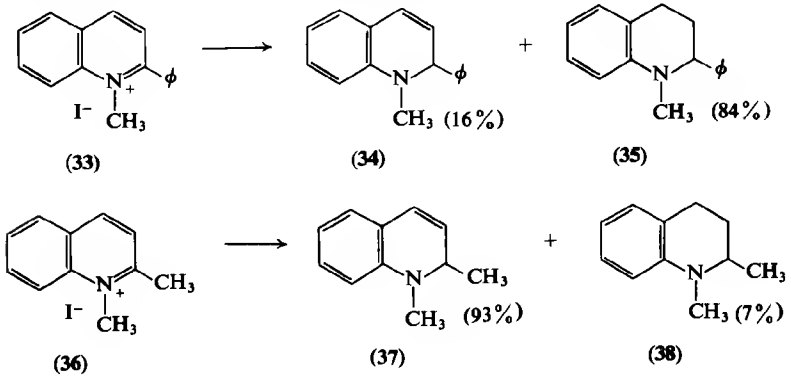


followed by protonation in the center of the dienamine system (**28**) to give a second iminium salt intermediate (**29**) and further reduction to give the observed tetrahydropyridine (**30**). The direct attack of a proton from solvent was shown by deuterium-labeling experiments. If only a molar equivalent of borohydride is used, a dihydropyridine can be isolated (*68,69*). Examples of isolation of the dihydroproduct are numerous and can be exemplified by reduction of N-benzyl-3-cyanopyridinium bromide (**31**) to the dihydro stage (**32**), which can be used directly in other reactions (*70*). Completely



reduced pyridines or piperidines have been reported (*57*) as well as 1,4 rather than 1,2 additions of hydride to give 1,4-dihydropyridines (*71*). Lyle and Anderson have provided the following correlations for sodium borohydride reduction of nitrogen heterocycles (*5*): the initial attack will occur at the C=N+ carbon if there is no steric interference; if there are severe steric interactions, attack will occur slowly or at another electrophilic position: The resulting dihydropyridine will be protonated by solvent provided that the position for attack is free of substitution and that the nitrogen is not conjugated to other π-electron systems; the resulting dihydropyridine can be intercepted by reaction with base: the resulting iminium intermediate is then further reduced to the tetrahydropyridine.

Lithium aluminum hydride reduction of pyridinium salts is very similar to sodium borohydride reduction and gives similar products, but the ratio of 1,2- and 1,4-dihydro- or tetrahydropyridines differs considerably (*5*). Isoquinolinium salts are reduced by sodium borohydride or lithium aluminum hydride in a manner identical to pyridinium salts (*5*). Quinolinium salts are reduced by sodium borohydride to give primarily tetrahydroquinolines (*72*) as shown by the conversion of **33** to **34** and **35**. When lithium aluminum hydride is used, the product is usually the dihydroquinoline (*73*) as shown in the conversion of **36** to **37** and **38**.

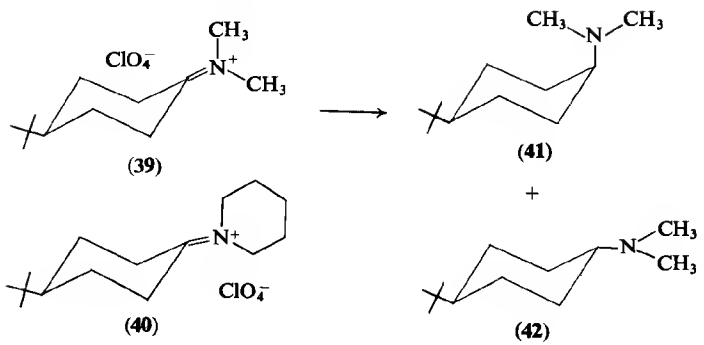


(33) (34) (35)

(36) (37) (38)

Examples of the reduction of other aromatic salts are given by Lyle and Andersen in their reviews of the subject (*5*) and by others (*74–80*).

The reduction of simple iminium salts, as expected, occurs in an analogous way. The reduction of **39** and **40** are of particular interest since they show that attack of aluminohydride occurs from the less hindered side of the molecule (*81*).

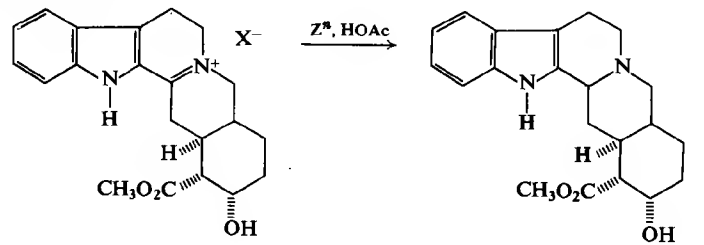


(39) (41) + (40) (42)

The stereochemistry of the reduction was found to be dependent on the concentration of the iminium salts **39** and **40** and on the ratio of iminium salt to LAH. When the reduction was carried out with a deficiency of LAH ($\frac{1}{4}$ mole of LAH per mole of iminium salt), the product ratio of **41**:**42** was 62:38. If an excess of LAH was present (10 moles of LAH per mole of iminium salt), the ratio of **41**:**42** was changed to 32:68.

Further examples of reduction of simple iminium salts are given in Table 7.

Dehydroyohimbine perchlorate (**43**) is reduced smoothly to **44** by Zn–HOAc (*90*).



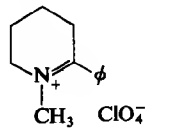
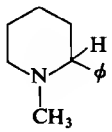
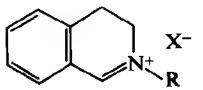
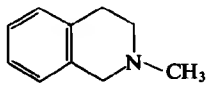
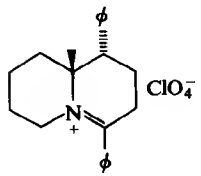
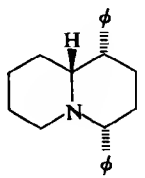
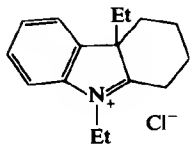
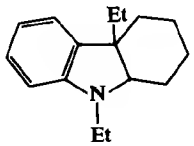
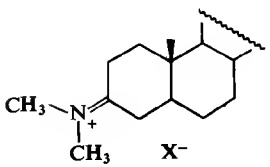
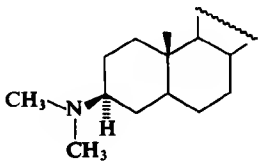
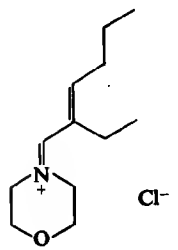
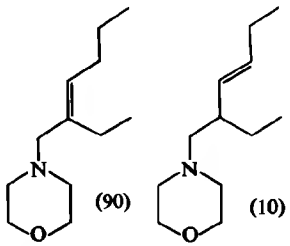
(43) (44)

Reduction of iminium salts with diborane and by the Meerwein–Ponndorf method have been reported (*89*).

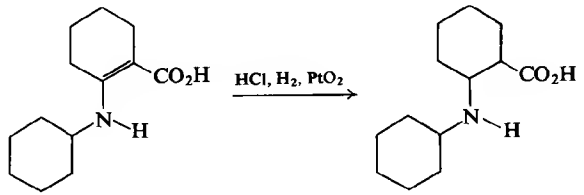
There have been only a few examples of reduction of the C=N+ function of catalytic hydrogenation since the reductions with complex hydrides are so easy to do in the laboratory. A possible reduction of an iminium salt **45** to **46** with platinum oxide was reported by McKay et al. (*91*). A report that platinum oxide reduces $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (**25**) in quantitative yield to **47** indicates that such reduction should be facile (*47*).

TABLE 7

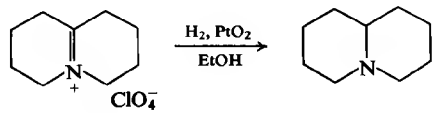
Reduction of Iminium Salts with Complex Hydrides

Compound	Product (yield, %)	Ref.
		*82*
		*83, 84*
		*85, 86*
		*87*
		*88*
		*89*
	(50) (97–60)	*89*
	(50) (3–40)	*89*

That $Pd/BaSO_4$ can be used is indicated by reduction of an intermediate in the synthesis of vasicine (*92*). Other examples of similar reductions are available in the literature (*93–94*).

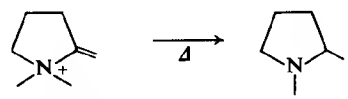


(45) (46)



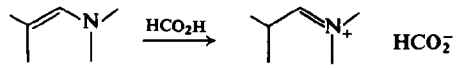
(25) (47)

The remaining major method for the reduction of the C=N+ functionality is the reaction with formic acid. The first report was that of Lukeš, who found (*95*) that thermal cleavage of 1,1-dimethyl-2-methylenepyrrolidinium formate was accompanied by reduction. Lukeš then explored the generality



(48) (49)

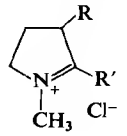
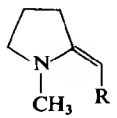
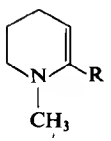
of the reaction as shown in Table 8 in a series of papers over many years (*96–99*). The reduction of enamines can be carried out easily since under the condition of the reaction (i.e., formic acid) the enamine is protonated.



That the reduction with formic acid proceeds by a hydride transfer reaction was proposed by Lukeš and Jižba (*100*) and finally proven by Leonard and Sauers (*63*). The use of variously deuterated formic acid allowed Leonard and Sauers to determine that: (1) protonation or

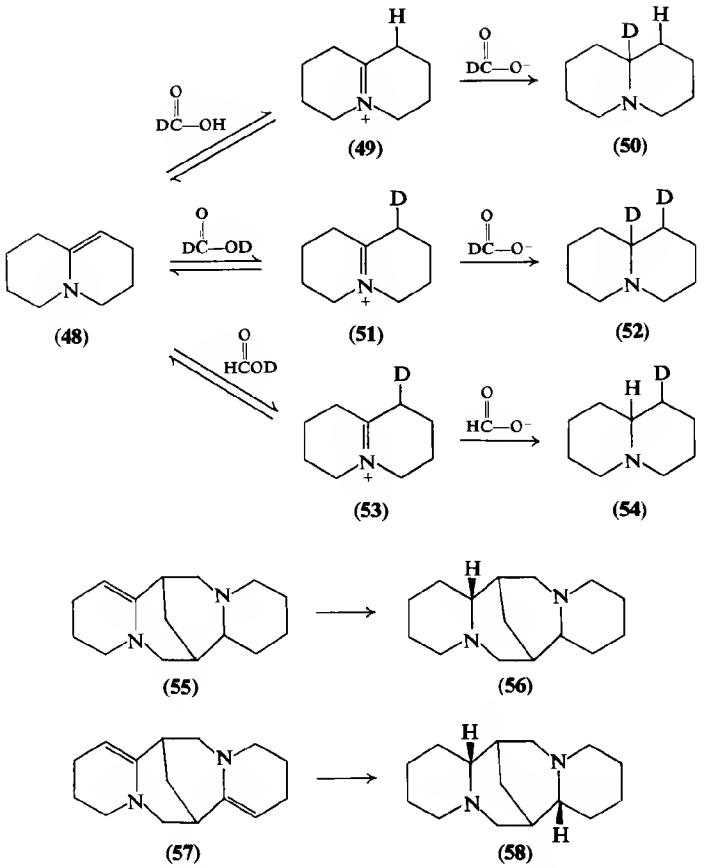
TABLE 8

Reduction of Iminium Salts with Formic Acid (*96–99*)

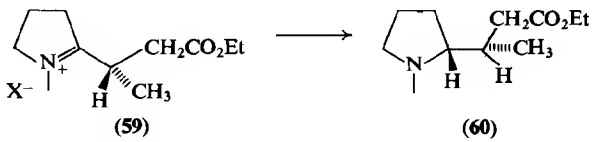
Compound	R	R′	Yield of tertiary amine, %
	H	Et	91
	H	2-Pr	94
	Me	Et	78
	Me	2-Pr	77
	Me	Pr	90
	Me	Me	76
	H	—	80
	Me	—	92
	CH_3	—	91
	Et	—	95
	Pr	—	96
	Bu	—	97
	Pent	—	92
	Benz	—	96
	$-(CH_2)_3CH{=}CH_2$	—	77

deuteration of **48** occurs first and is a reversible process; (2) deuteration (**51**, **53**) or protonation occurs at the β-carbon atom; (3) reduction of hydride transfer occurs from the formic (*d*) acid to the 10 position, exclusively. These facts are only compatible with a mechanism as shown above in the formation of **50**, **52**, **54**. The preformed iminium perchlorate was reduced in equal or in better yield (73% compared to 58–65% for the enamine). The nature of the hydride transfer agent is not known, but is presumed to be a formate or a formate ion pair or some formate ester (*63*).

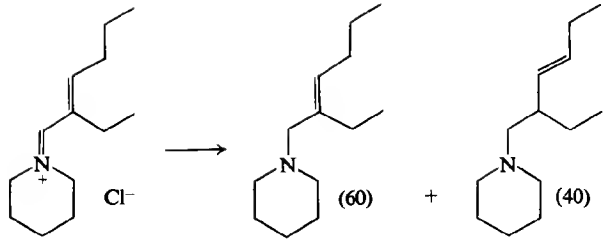
The reaction can be shown to have good stereospecificity in the conversion of (−)-Δ^5-dehydrosparteine (**55**) and (−)-$\Delta^{5,11}$-didehydrosparteine (**57**) to (−)-sparteine (**56**) and (−)-α-isosparteine (**58**) (*46,101*).



Another example (*102*) of selective reduction in a simpler system is shown by the conversion of **59** to **60**.

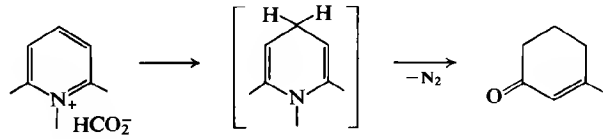


Dienamines, for example, **61**, have been reported (*89*) to be reduced by formic acid to give a mixture of products **62** and **63** in 21% yield.



(61) (62) (63)

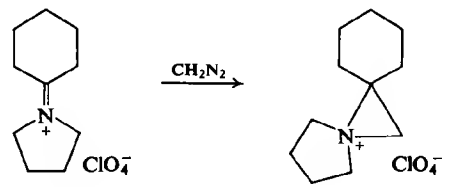
Lukeš and Jižba (*100*) have reported that 1,2,6-trimethylpyridinium formate (**64**) is reduced at the 4 position and eventually gives a product 3-methylcyclohex-2-enone (**65**).



(64) (65)

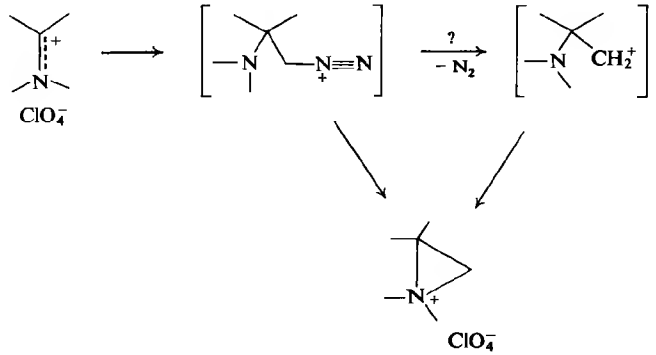
C. Addition of Diazoalkanes

Another class of nucleophilic addition to iminium salts can be found in the addition of diazoalkanes. These are of great interest since they were known to add and then react further to form three-membered rings as in the case of C=S, C=O, and C=C functions (*103*). Leonard and Jann (*104–106*) found that treatment of iminium perchlorates with diazomethane and other diazoalkanes yielded aziridinium salts. Treatment of an iminium salt such as N-cyclohexylidinepyrrolidinium perchlorate (**66**) with diazomethane yielded a new product whose structure was established by spectral and chemical means to be 5-azoniadispiro[4.0.5.1]dodecane perchlorate (**67**). The UV spectrum was devoid of any absorption above

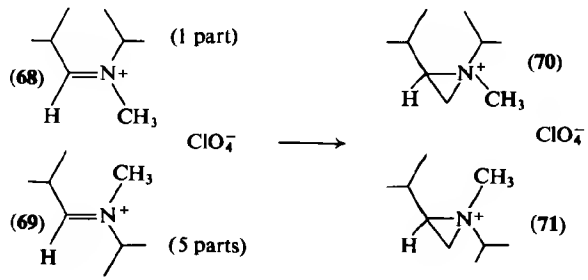


(66) (67)

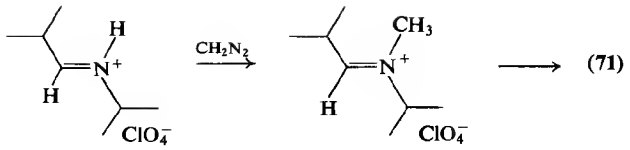
200 mμ. The infrared spectrum did not show C—N+ or ⁺N—H. The molecular weight was consistent only with monomeric species and the NMR spectrum showed the presence of a new singlet at $\tau = 6.98$ whose integrated area corresponded to two hydrogen atoms. The product reacted with thiosulfate in a manner analogous to that observed for aziridinium intermediates (*107,108*). The postulated mechanism involves nucleophilic attack on the iminium moiety followed by loss of nitrogen and ring closure to give the aziridinium salt (*109*).



It is not known whether the amine assists the elimination of the nitrogen, but that the iminium salt retains its stereochemistry has been demonstrated (*109*). When a mixture of **68** and **69** of 1:5 ratio is treated with diazomethane, the ratio of **70**:**71** obtained in 75% yield and determined spectroscopically was still 1:5. The *trans*-N-isopropyl-N-methylisobutylidinium perchlorate (**69**) was prepared by alkylation of an aldimine salt with diazomethane and

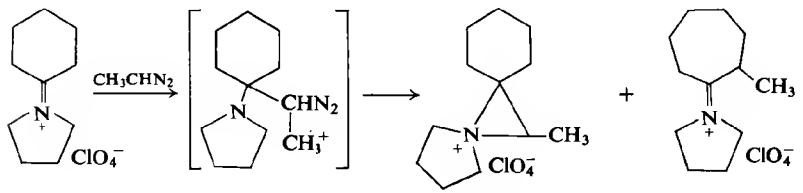


then by further reaction with diazomethane to give **71** so that the spectral assignments for determining *cis-trans* ratios are on a firm ground.

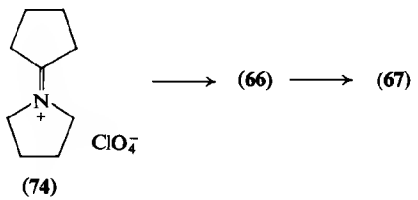


(69)

The lifetime of the diazomethane adduct is not known, but it must be of sufficient length that carbon can compete with nitrogen in participation as a nitrogen molecule leaves (*24,109*). The reaction of **66** with diazoethane yields **72**, the normal adduct, and **73**, the product from ring expansion. The structure of **73** was determined by hydrolysis to 2-methylcycloheptanone. In a similar reaction **74** yields **67** directly without isolation of **66**. A similar ring expansion has been observed for cyclooctanone derivatives (*16*).

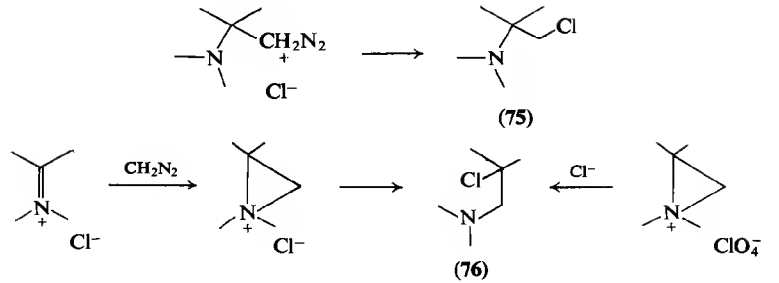


(66) (72) (73)



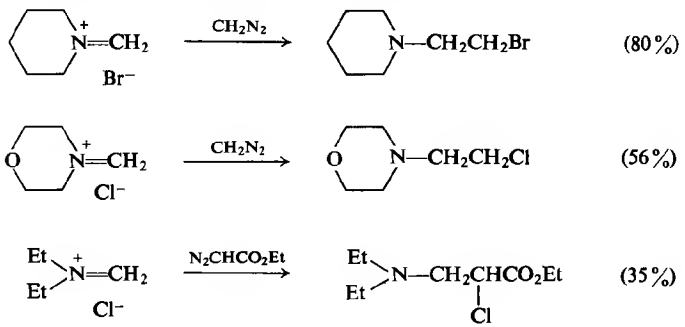
(74)

Opitz and Griesinger (*16*) investigated the reaction of diazomethane and iminium chlorides, but because of the nucleophilicity of the chloride ion they obtained only β-chloroamines. The amines were assumed to result from collapse of a carbonium ion with a chloride ion and have structure **75**. Further investigation (*110*) has shown that an aziridinium intermediate was formed first and was then opened to give β-chloroamines that were isomeric (**76**) with the structures (**75**) proposed by Opitz and Griesinger. It was also shown (*110*) that iminium chlorides with diazomethane give the same products as opening of corresponding aziridinium perchlorates with



(75) (76)

chloride ion. All of the structures were established beyond a reasonable doubt by spectral methods (*110*). The synthesis of β-chloroamines by reaction of α-chloroamines with diazomethane had been observed earlier, but the presence of the aziridinium intermediate had not been detected (*111*).



A representative list of aziridinium salts prepared by reaction of iminium salts with diazomethane is given in Table 9. The reactions of aziridinium salts are many and varied, but will not be given here since their synthetic utility has been explored and reported elsewhere (*109,112–114*). The products from the reaction of iminium chlorides and diazomethane are reported in Table 10. Many more examples are available in the literature (*16*).

D. Addition of Other Nucleophiles

The reaction of a large number of other nucleophiles with iminium salts will at least be mentioned in this section. Among the nucleophiles which react with iminium salts are cyanide (*48,115–119*), mercaptide (*48*), alkoxide (*48*), amine (*120*), azide (*44*), phosphine (*44*), and phosphate ester (*44*). One can say with little reservation that almost all nucleophiles will react

TABLE 9

Reaction of Iminium Salts with Diazomethane

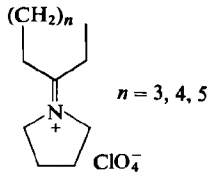
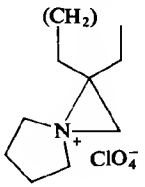
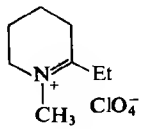
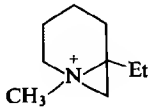
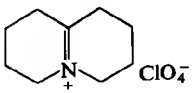
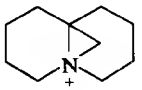
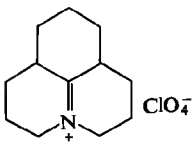
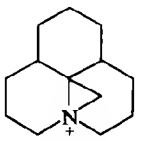
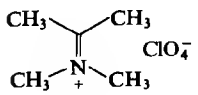
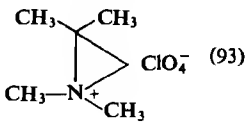
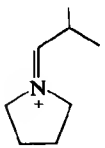
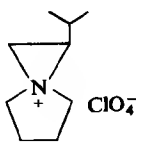
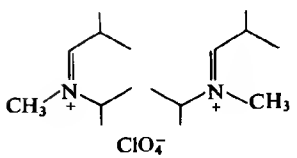
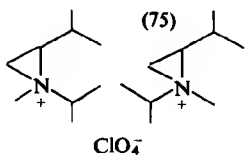
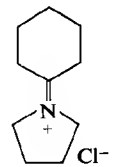
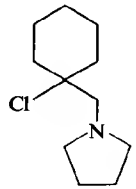
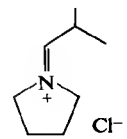
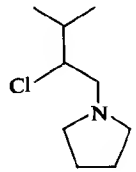
Iminium salt	Product (yield, %)	Ref.
	 (93) (99) (79)	*104–106* *28*
	 (87)	*113*
	 (90)	*113*
	 (72)	*113*
	 (93)	*28*
	 (85)	*28*
	 (75)	*109*

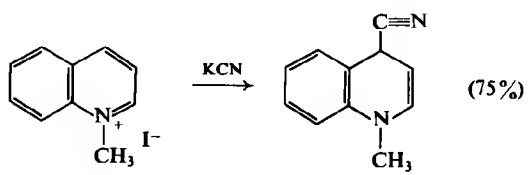
TABLE 10

Reaction of Iminium Chlorides with Diazomethane

Compound	Product	Ref.
		*16,110*
		*16,110*

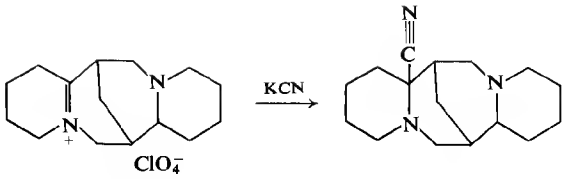
with iminium salts and that only the product stability will determine whether the adducts can be isolated.

The addition of cyanide was first examined by Kaufmann (*115–119*), who found that aromatic iminium compounds such as quinolinium methiodide (**77**) added potassium cyanide to give 1,4-addition product **78**.



(**77**) (**78**) (75%)

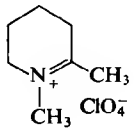
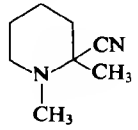
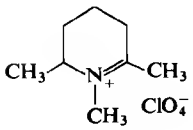
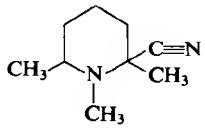
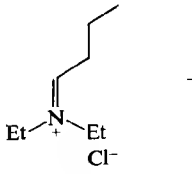
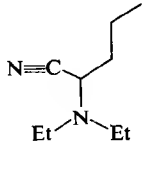
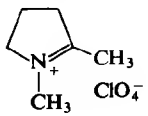
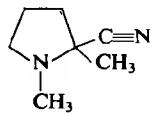
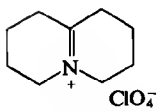
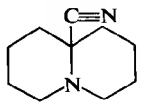
The reaction has been examined more recently by several groups with simple iminium salts and the results are analogous. Treatment of $\Delta^{1(6)}$-dehydrosparteinium perchlorate (**79**) gave (–)-6-cyanosparteine (**80**) (*46*). Other examples of this reaction are listed in Table 11.



(79) (80)

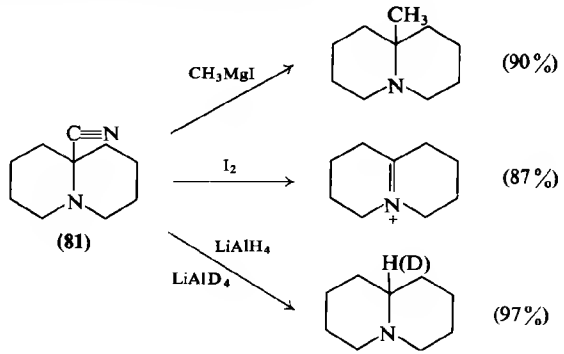
TABLE 11

Addition of Cyanide to Iminium Salts

Compound	Product	(yield, %)	Ref.
		(97)	*121*
		(82)	*121*
		(21)	*44*
		(70)	*122*
		(88)	*48*

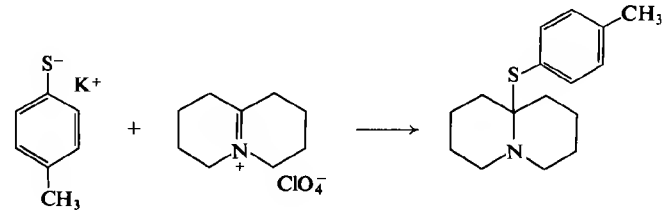
The cyano group can enter into a number of reactions, including elimination to give the iminium salts (*10,48,63*).

The cyano group can enter into a number of reactions, including elimination to give the iminium salts (*10,48,63*).



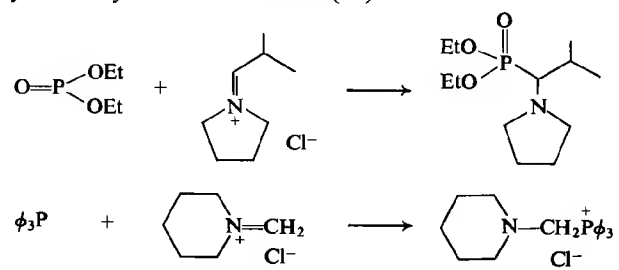
(81)

Mercaptides and alkoxides have been shown to react with iminium salts, but the products have been shown to be unstable (*48*). Only one compound has been isolated and characterized and that is the adduct of *p*-thiocresol potassium salt. The adduct (**82**) decomposed on standing in air or on treatment with dilute acids to give back the *p*-thiocresol (*48*).

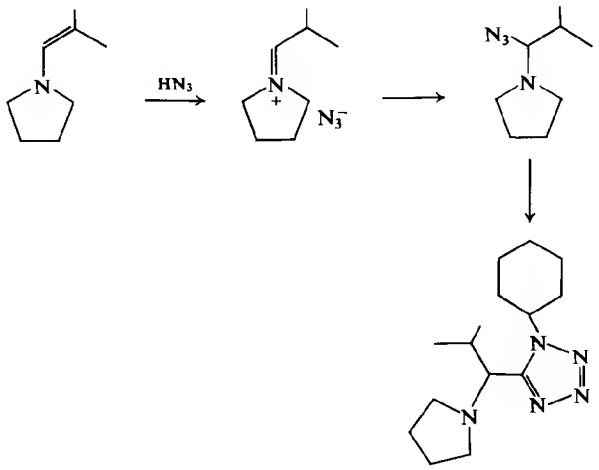


(25) (82)

Dialkyl phosphites and phosphines have been shown to react with iminium salts. There are only a few examples of such reactions so that the generality has not yet been determined (*44*).

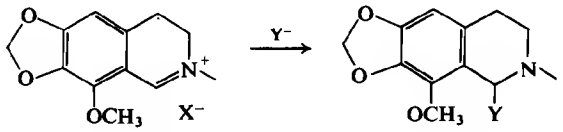


Azides have been shown to react with iminium salts to give addition products. The same product is obtained if the iminium salt is treated with azide ion or if the enamine is treated with hydrazoic acid (*14*). The yields of the products were all very high (85–95%). The interest in this reaction centers on the fact that the azides react with isonitriles to give substituted tetrazoles (**83**) (*44*).



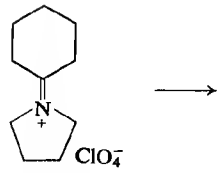
(**83**)

The reaction of other nucleophiles such as amines (*123,124*), hydroxylamines, various carbanions, and hydroxide (*120*) have been tried but not examined in detail. Hydrolysis of iminium salts is covered elsewhere (*125*).

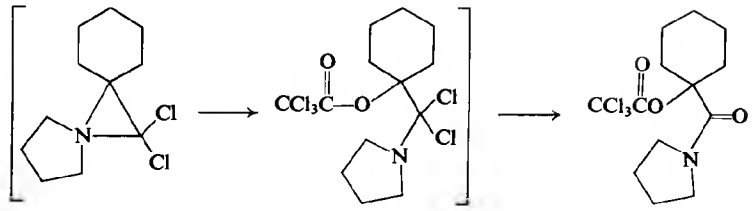


Y = $^-$OH, $^-$NHOH, $^-$NHϕ, $^-CH_2CO_2H$, $^-CH_2COCH_3$

The reaction of iminium salts such as **66** with salts of trichloroacetic acid has been shown to yield amides such as **84** on hydrolysis (*126*). It was suggested that the reaction proceeds by addition of dichlorocarbene to give an aziridinium intermediate (**85**), which was opened by trichloroacetate followed by hydrolysis to give the observed products (*126*). The observed products from the reaction can be accounted for by formation of CCl_3^-,

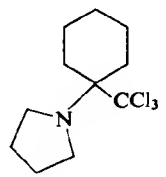


(**66**)



(**85**) (**84**)

which could add to the C=N+ to give **86** (*127–132*) followed by displacement of chloride to give the aziridinium intermediate in a process analogous to that reported for other β-chloroamines (*110*). The conversion of **85** to **84** would follow by known steps.

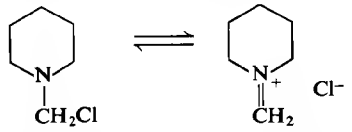


(**86**)

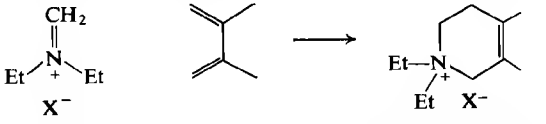
IV. Addition of Nucleophiles to Iminium Intermediates

The previous sections have dealt with stable C=N+ functionality in aromatic rings as simple salts. Another class of iminium salt reactions can be found where the iminium salt is only an intermediate. The purpose of this section is to point out these reactions even though they do not show any striking differences in their reactivity from stable iminium salts. Such intermediates arise from α-chloroamines (*133–135*), isomerization of oxazolidines (*136*), reduction of α-aminoketones by the Clemmensen method (*137–139*), reductive alkylation by the Leuckart–Wallach (*140–141*) or Clarke–Eschweiler reaction (*142*), mercuric acetate oxidation of amines (*46,93*), and in reactions such as ketene with enamines (*143*).

α-Haloamines have been prepared primarily by Bohme, who has examined their usefulness in detail. The α-haloamine is presumed to exist in rapid equilibrium with the iminium salt, which is the reactive species.

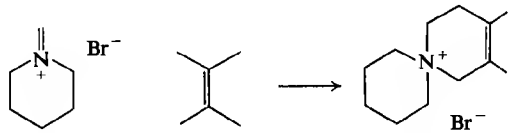


The reactions with nucleophiles include a wide variety such as amines, sulfides (*133,135*), diazomethane (*111*), and others. Of particular interest were the reactions of such intermediate iminium salts with 2,3-dimethylbutadiene to give cyclic products as shown in the reaction of N-bromomethylpiperidine and N-bromo- and N-chloromethyldiethylamine (*134*).



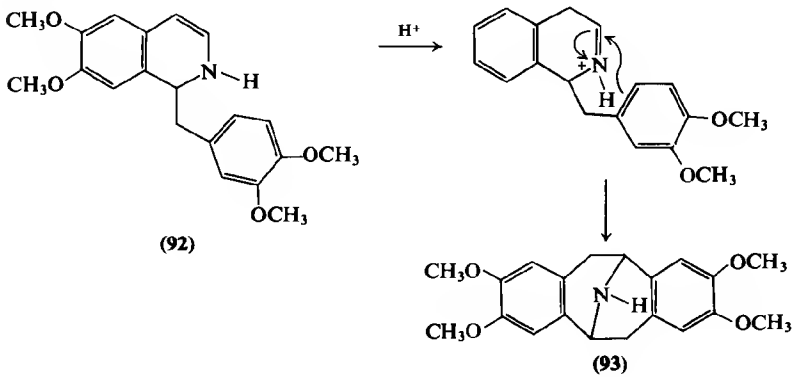
(87)

(88) X = Cl (74%)
(89) X = Br (69%)



(90) **(91)**

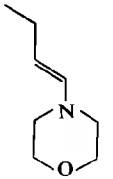
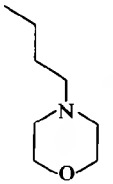
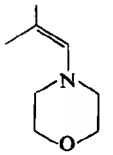
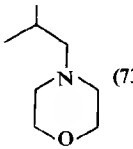
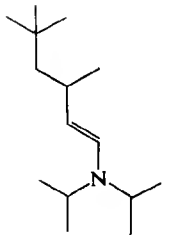
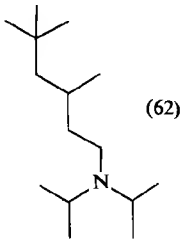
A cyclic intermediate has been proposed (*144*) in the conversion of **92** to **93**.



(92) **(93)**

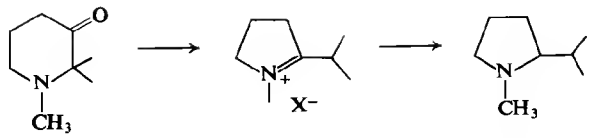
It has been shown (*140*) that enamines react as well, if not better, under the conditions of the Leuckart–Wallach reaction to give amines than do ketones in the presence of ammonia, primary amines, or secondary amines. This implies that in the Leuckart–Wallach reaction the pathway may be through the enamine and, of course, the iminium salt. The Leuckart–Wallach reaction has been reviewed (*141*). Examples of enamines reduced under the conditions of the Leuckart–Wallach reaction are listed in Table 12.

TABLE 12

Compound	Product (yield, %)	Ref.
	 (54)	*140*
	 (73)	*140*
	 (62)	*140*

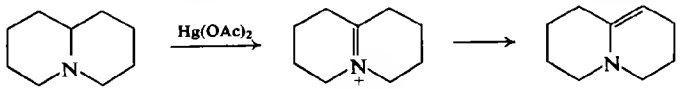
The reductive alkylation reaction under Clarke–Eschweiler conditions has been shown to proceed through an iminium intermediate (*142*).

Clemmensen reductions of α-aminoketones that proceed with ring enlargement or ring contraction are presumed to proceed by an iminium intermediate. This reaction has been examined in detail (*137–139*), and an example is given in the conversion of (**94**) to an iminium intermediate (**95**), which is reduced to **96**.

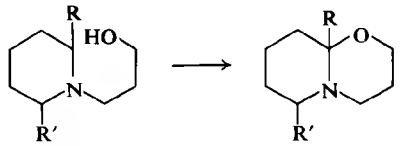


(94) (95) (96)

Another iminium intermediate that has been proposed is in the mercuric acetate oxidation of amines (*46,93*). This reaction is discussed in the

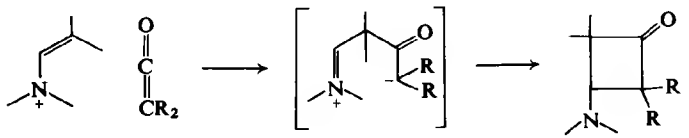


chapter on the synthesis of enamines since the enamines usually are the final products. When a β- or γ-amino alcohol (**97**) is treated under the above conditions, the products are oxazolidines or 1,3-oxazines (*145*) such as **98**. In this case one can look on the reaction as oxidation of the amine to the iminium salt and addition of the alcohol to give the oxazolidine or 1,3-oxazine, **98**.



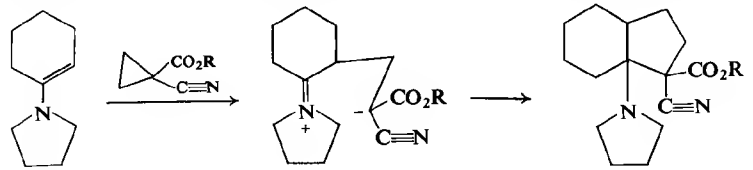
(97) (98)

The reaction of enamines with ketene (*146*) and sulfene (*147*) are presumed to proceed by a two-step process involving an iminium intermediate such as **99**. In fact, reaction with all electrophilic olefins such as acrylonitrile and related reagents could be thought of as going through an iminium intermediate similar to **99**. Another example is given by addition to an enamine



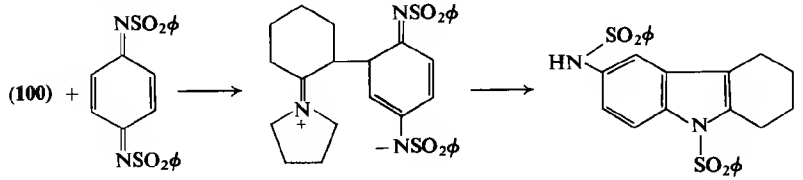
(99)

(**100**) of a cyclopropane derivative (*148*) with formation of a five-membered ring (**101**). Other electrophiles such as quinoneimine dibenzenesulfonamide



(100) (101)

reacted with enamines such as **100** to give **102**, which could be explained as arising from an intermediate iminium salt (*143*).



(102)

As shown in the preceding pages, the uses that iminium salt chemistry has been put to are highly diversified. This elaboration of reactions should continue for a long time for there are some problems in iminium salt chemistry that are not answered and many questions that have not even been asked. The uses that iminium salts will be put to in the future as reaction intermediates are limited only by the ingenuity of chemists.

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6

CYCLOADDITION REACTIONS OF ENAMINES

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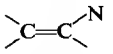
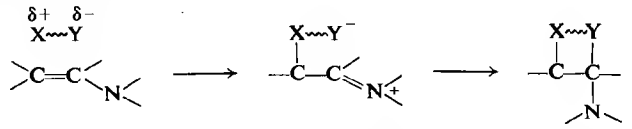
I. Introduction

Most of the reactions described in this chapter would fall under Huisgen's definition of a cycloaddition reaction (*1*, *1a*). However some of the reactions described would not be considered cycloaddition reactions according to this restrictive definition. Therefore, the more liberal definition given by Baldwin will be used as a guideline, namely, "Cycloadditions are chemical transformations giving at least one product having at least two new bonds as

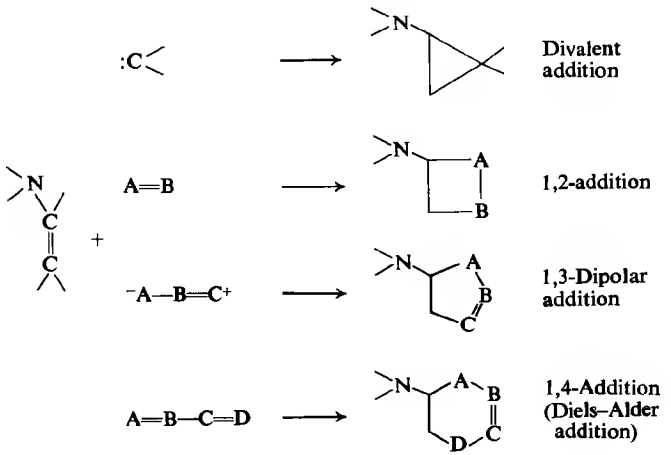
constitutents of a new ring" (*2*). The carbon atoms of the enamine functional group alone



are the sites of attack and hence provide the two carbon cyclization bridge in most of the reactions described, although a few reactions involve an adjacent functional group along with the enamine. In some of the reactions it has not been established whether the cycloaddition involves a concerted mechanism or a stepwise ionic mechanism, although the latter seems generally to be the favored pathway. Stepwise ionic cycloaddition involves an initial electrophilic attack at the β position of the enamine (since addition to the nitrogen atom is rapidly reversible and hence unimportant here) followed by a nucleophilic attack at the enamine's α position.



The types of cycloadditions discovered for enamines range through a regular sequence starting with divalent addition to form a cyclopropane ring, followed by 1,2 addition (*3*) of an alkene or an alkyne to form a cyclocyclobutane or a cyclobutene, then 1,3-dipolar addition with the enamine the dipolarophile (*4*), and finally a Diels–Alder type of reaction (*5*) with the enamine the dienophile.

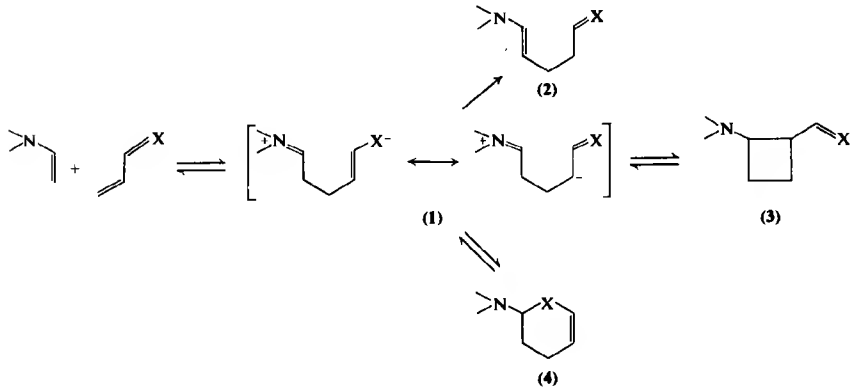


II. Carbocycloadditions

A. Electrophilic Alkenes

1. *Introduction*

The reactions of electrophilic alkenes (alkenes attached to electron-withdrawing groups) with enamines produce one or more of the following products: simple alkylation (**2**), 1,2 cycloaddition (**3**), and 1,4 cycloaddition (**4**). Competition with C alkylation by N alkylation is inconsequential and therefore will be largely ignored (*6,7*). A stepwise ionic mechanism leading to these products necessarily involves the formation of a zwitterion intermediate (**1**) as the first step, which is then followed either by one of the

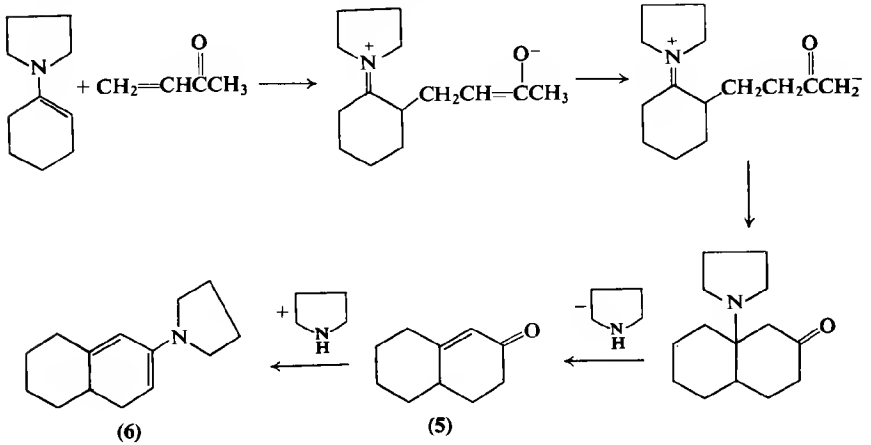


two possible cycloadditions to give a cyclic molecule or proton elimination–addition to give a simple alkylated molecule. This proton elimination–addition has been observed to be intramolecular in one example studied (*8*). It has been shown in some cases that the cyclobutyl form (**3**) must lie somewhere along the pathway between starting materials and simple alkylated product (*9*). It probably exists as a branch that is in equilibrium with a common intermediate, namely, zwitterion **1**. The 1,4-cycloaddition product (**4**) also seems to be in equilibrium with this zwitterion intermediate (**1**) (*10,11*).

2. *Conjugated with Carbonyl Group*

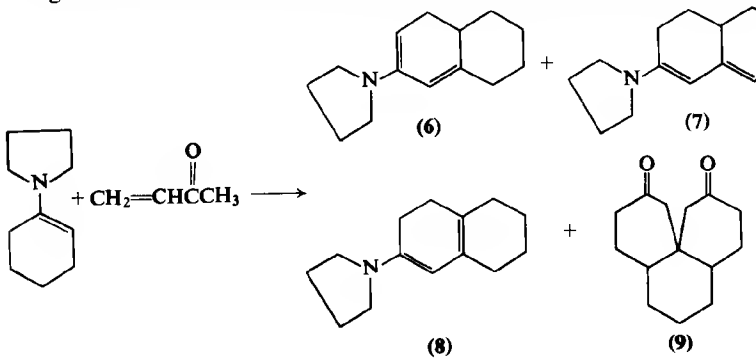
The first reported cyclization involving an enamine was the 1,4 cycloaddition of methyl vinyl ketone with the enamine of cyclohexanone to give,

after hydrolysis, $\Delta^{1,9}$-octal-2-one (**5**) (*6,7,12*). This reaction has been used a great deal in synthetic sequences (*13–15b*). It was reported that isomeric octalones were also formed during this reaction along with some disproportionation products (*16*). Subsequently it was determined that two isomeric enamines (**6**, **7**) and possibly a third (**8**) were produced before hydrolysis along with diketone **9**, but no disproportionation products were observed (*17*). These "disproportionation" products may have arisen from the reduction of the enamine by some excess secondary amine (*18*). This is a definite option since the oxidation product from the proposed disproportionation reaction apparently was not isolated (*19*). The 1,4 cycloalkylation can be described by the following mechanism:



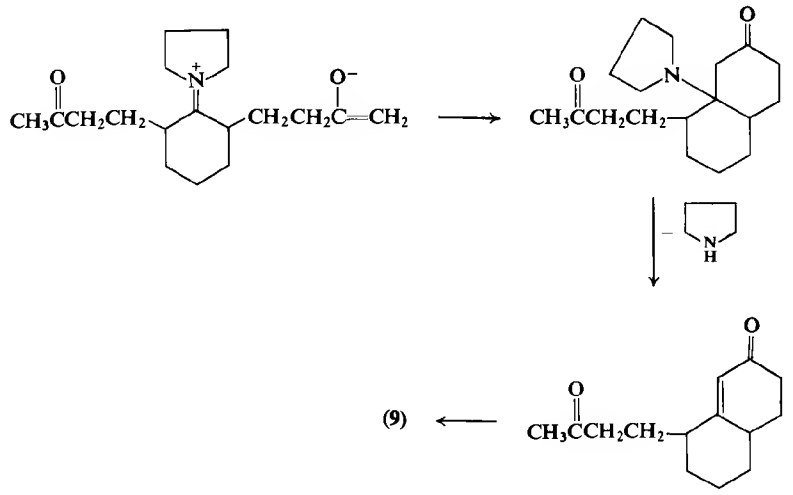
(6) (5)

The amount of diketone **9** formed during the reaction could be enhanced by using no solvent or ethanol solvent in place of benzene solvent. The use of



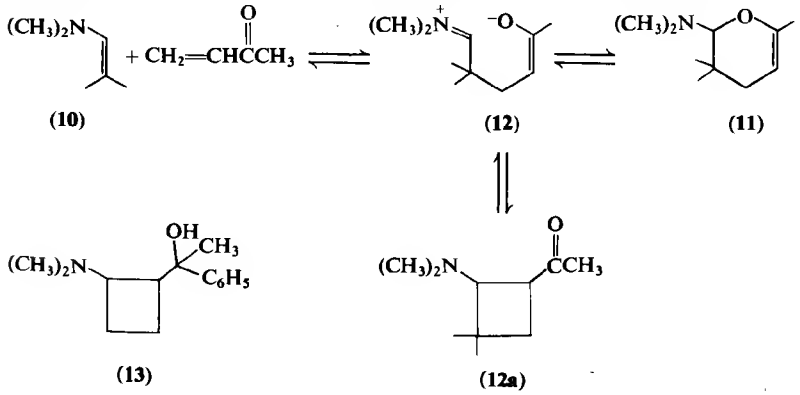
(6) (7) (8) (9)

ethanol solvent favors dialkylation of enamines (*7,19,20*). It was shown that enamines **6**, **7**, and **8** are not precursors for **9**. Therefore the following is a likely mechanism (starting with the disubstituted product):



(9)

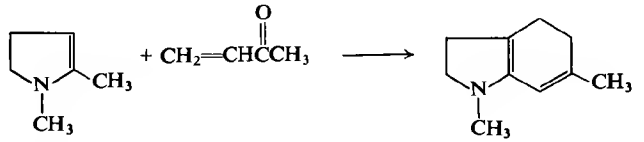
The initial product formed when methyl vinyl ketone is mixed with an enamine [such as N,N-dimethylisobutenylamine (**10**)] is the dihydropyran (**11**) from a 1,4 cycloaddition (*11,20a,20b*). The chemical reactions that the dihydropyran undergoes indicate that it is readily equilibrated with the cyclobutane isomer **12a** and zwitterion **12** (*11*). Treatment of adduct **11** with phenyllithium gives cyclobutane **13**, possibly via intermediate **12a** (*11*).



(10) (12) (11) (13) (12a)

At higher temperatures the mixture of **10** and methyl vinyl ketone yields the 1,4-carbocyclic compound as described previously. Methyl isopropenyl ketone (*6*), ethyl acetylacrylate (*6*), 2-cyclohexenone (*21*), and 1-acetyl-1-cyclohexene (*22*) also undergo this type of cyclization reaction with enamines at higher temperatures. This cycloalkylation reaction occurs with enamines made of strongly basic amines such as pyrrolidine, but the less reactive morpholine enamine combines with methyl vinyl ketone to give only a simple alkylated product (*7*). Chlorovinyl ketones yield pyrans when allowed to react with the enamines of either alicyclic ketones or aldehydes (*23*).

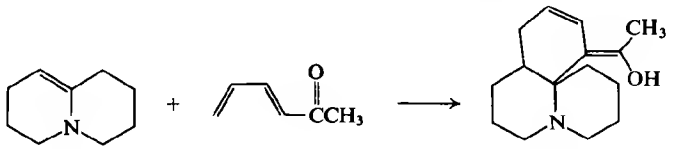
Heterocyclic enamines often undergo two-step "1,3 cycloaddition" with methyl vinyl ketone. This involves electrophilic attacks by an olefinic carbon and by a carbonyl carbon (*24,25*). For example, 1,2-dimethyl-Δ^2-pyrroline (**14**), when treated with methyl vinyl ketone, produces 1,6-dimethyl-2,3,4,5-tetrahydroindole (**15**) (*24*). The requirement which must be met so that this type of cyclization reaction can take place is that the α position of the heterocyclic enamine be carbon substituted. This provides



(**14**) (**15**)

the possibility for an isomeric enamine. This isomeric enamine, in the second step of the reaction, undergoes electrophilic attack by the side-chain carbonyl group.

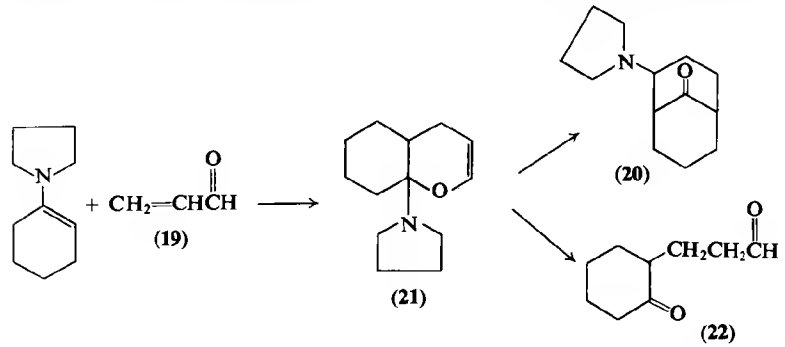
The vinylogous 3,5-hexadien-2-one (**16**) adds in a 1,4 cycloaddition with Δ^2-dehydroquinolizidine (**17**) to form compound **18** (*26*). A similar 1,4-cycloaddition reaction takes place between pyrylium salts and the pyrrolidine or morpholine enamines of cycloalkanones (*26a*).



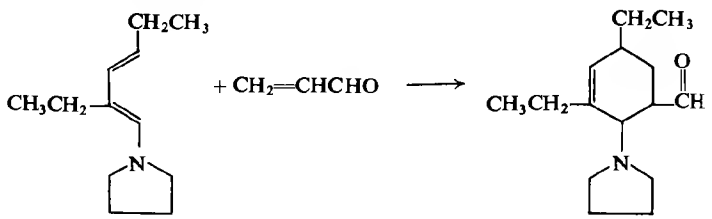
(**17**) (**16**) (**18**)

Acrolein (**19**), when allowed to react with an enamine such as the pyrrolidine enamine of cyclohexanone at room temperature followed by distillation, gives an interesting bicycloaminoketone (**20**) in a 75% yield (*27*). This

reaction has proved to be a very useful one for ring expansions. The mechanism of this two-step 1,3-cycloaddition reaction was first studied by Untch (*28*). He showed that, following the first electrophilic attack, the reaction occurred intermolecularly with transfer of the amine from the ketonic enamine to the aldehyde followed by cyclization. For cyclohexanone enamines the initial product formed is dihydropyran (**21**) (*29*). Distillation of this product produces bicycloaminoketone **20**, the stereochemistry of which has been studied (*29a*). A mixture of stereoisomeric bicycloamino-



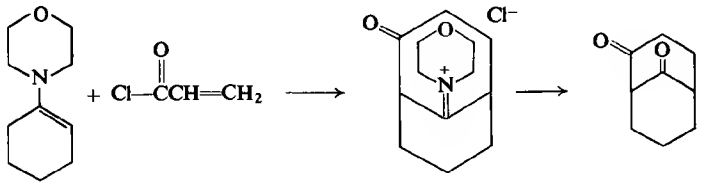
ketones consisting primarily of the endo isomer is obtained from this distillation when N-phenylpiperazine is the amine (*29*). Hydrolysis of dihydropyran **21** yields ketoaldehyde **22** (*30*). Cyclopentanone and cycloheptanone enamines give bicycloaminoketones directly with no dihydropyran intermediates when treated with acrolein (*29*). Dihydropyrans alone are found when aldehyde enamines (either with or without β-hydrogen atoms) and acrolein are allowed to react (*10,31*). The electron-poor acrolein becomes the dienophile when it is allowed to react with electron-rich dienamines. This is illustrated by the reaction between acrolein and 1-N-pyrrolidino-2-ethyl-1,3-hexadiene (**23**) to give 2-N-pyrrolidino-3,5-diethyl-Δ^3-tetrahydrobenzaldehyde (**24**) (*10*).



(**23**) (**24**)

A substituted α,β-unsaturated aldehyde, cinnamaldehyde, has been observed to undergo the same type of two-step 1,3-cycloaddition reaction with a cyclohexanone enamine as acrolein does, forming in this case a stereoisomeric mixture of substituted bicycloaminoketones in excellent yield (*29a,31a,31b*).

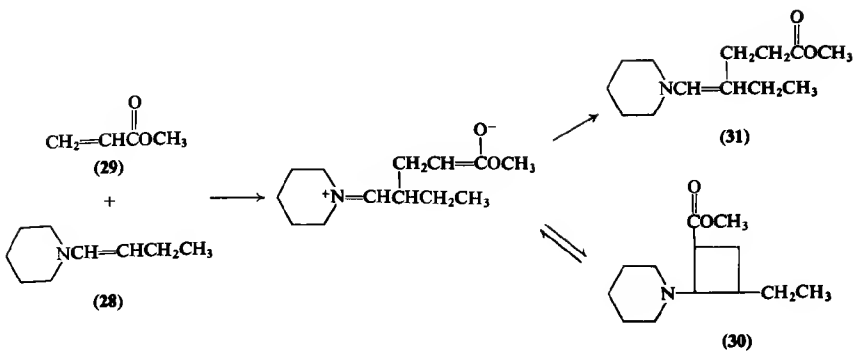
Acryloyl chloride can be used to cause ring enlargement with the production of a bicyclodiketone when it is treated with a cyclohexanone enamine. This is shown by the reaction of acryloyl chloride (**25**) with 1-N-morpholino-1-cyclohexene (**26**), affording diketone **27** upon hydrolysis (*32,33*).



(26) (25) (27)

The reaction of methyl or ethyl acrylate with the enamine of an alicyclic ketone results in simple alkylation when the temperature is allowed to rise uncontrolled in the reaction mixture (*7,34,35*). If the reaction mixture is kept below 30°C, however, a mixture of the simple alkylated and cyclobutane (from 1,2 cycloaddition) products are obtained (*34*). Upon distillation of this mixture only starting material and simple alkylated product is obtained because of the instability of the cyclobutane adduct.

Enamines of aldehydes or acyclic ketones undergo exclusive 1,2 cycloaddition when treated with acrylate esters below 30°C (*9,36,37*). Simple alkylation of enamines by electrophilic olefins depends on the presence of a β hydrogen in the enamine. Therefore it would be expected that the cyclobutane adduct of an enamine with no β hydrogens and an acrylate ester should be stable with respect to the simple alkylated product. This is borne out in fact since these adducts can be distilled with no apparent decomposition (*36–40*). Those adducts from enamines which have β hydrogens decompose into starting materials and simple alkylation products when heated above about 125°C (*37*). The cyclobutane adduct has been shown to lie along the pathway between starting materials and simple alkylation product (*9*), probably as a branch that is in equilibrium with a common zwitterion intermediate. For example, when the piperidine enamine of butyraldehyde (**28**) is allowed to react with methyl acrylate (**29**) the 1,2 cycloadduct (**30**) forms initially and reversibly. Raising the temperature



(29) (28) (31) (30)

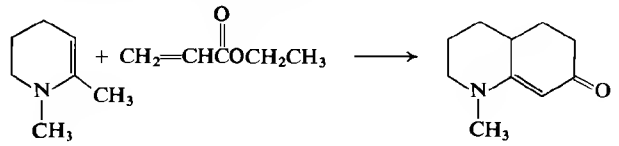
of the reaction mixture produces the simple alkylated product **31** (*37*). Steric requirements for 1,2 cycloaddition seem to be stringent since methyl methacrylate, methyl crotonate, or methyl cinnamate do not form an isolatable cyclobutane adduct with an enamine (*9,37*).

In a similar manner diethyl maleate (actually diethyl fumarate since the basic enamine catalyzes the maleate's isomerization upon contact) forms unstable 1,2 cycloadducts with enamines with β hydrogens at temperatures below 30°C (*37*). At higher temperatures simple alkylated products are formed (*41*). Enamines with no β hydrogens form very stable 1,2 cycloadducts with diethyl maleate (*36,37,41*). The two adjacent carboethoxy groups of the cyclobutane adduct have been shown to be *trans* to one another (*36,37*).

Two-step 1,4 cycloaddition of enamines, such as was observed with methyl vinyl ketone, is not possible with acrylate or maleate esters. This is due to the fact that, following the initial simple substitution, no side-chain carbanion is available for nucleophilic attack on the α carbon of the iminium ion. Likewise two-step 1,3 cycloaddition, such as that found when alicyclic enamines were treated with acrolein, is impossible with acrylate or maleate esters because transfer of the amine moiety from the original enamine to the side chain to form a new enamine just prior to the final cyclization step is not possible. That is, the reaction between a secondary amine and an ester does not produce an enamine.

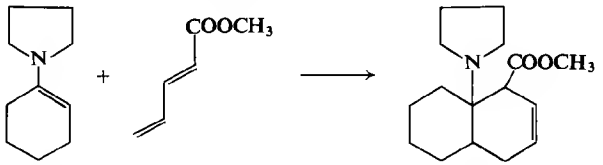
If the α position of an enamine is carbon substituted, providing the possibility of an isomeric enamine, and if the amine group and other substituent groups are sufficiently removed from the sites of electrophilic attack as to not cause any steric interference, then simple alkylation of an enamine by an acrylate ester can be followed with a second electrophilic

attack by the carbonyl group on the isomeric enamine to form a two-step 1,3-cycloaddition product. α-Substituted heterocyclic enamines completely fulfill these requirements and hence undergo this type of cycloaddition with acrylate esters (*25,42–45*). For example, the reaction between 1,2-dimethyl-Δ^2-tetrahydropyridine (**32**) and ethyl acrylate resulted in the formation of cyclization product **33** (*44*).



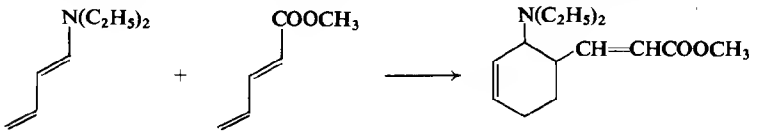
(**32**) (**33**)

Enamines have been observed to act both as dienophiles (*46–48*) and dienes (*47,49*) (dienamines in this case) in one-step, Diels–Alder type of 1,4 cycloadditions with acrylate esters and their vinylogs. This is illustrated by the reaction between 1-(N-pyrrolidino)cyclohexene (**34**) and methyl *trans*-2,4-pentadienoate (**35**), where the enamine acts as the dienophile to give the adduct **36** (*47*). In a competitive type of reaction, however, the



(**34**) (**35**) (**36**)

electron-rich dienamine preferentially acts as the diene, with the electron-poor pentadienoate ester acting as the dienophile, as is shown by the reaction

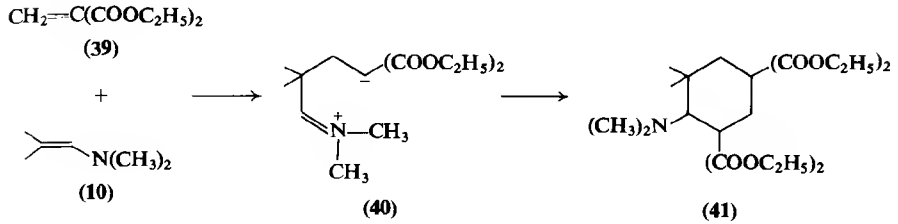


(**37**) (**35**) (**38**)

between methyl *trans*-2,4-pentadienoate (**35**) and 1-diethylamino-1,3-butadiene (**37**) to give product **38** (*47*). A similar reaction has been observed between α-chloroacrylonitrile and the dienamine 1-N-(morpholino)-1,3-butadiene. Upon attempted vacuum distillation of the reaction product,

hydrogen cyanide and hydrogen chloride were eliminated to finally produce N-phenylmorpholine hydrochloride (*49a*).

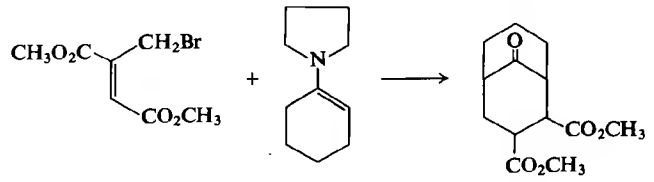
Sometimes a 2:1 adduct is formed between enamines and unsaturated esters instead of the usual 1:1 adduct. This is the case when N,N-dimethyl-isobutenylamine (**10**) is allowed to react with diethyl methylenemalonate (**39**) producing compound **41** (*37*). This product is formed even when an



(**39**) (**10**) (**40**) (**41**)

excess of enamine is present. The ease of formation of this 2:1 adduct is probably due to the stabilizing effect of the adjacent ester groupings on the anionic center in intermediate **40** and to the minimal steric requirements of the incoming electrophilic olefin (*37*).

A two-step cyclization of an enamine with an electrophilic olefin has been reported in which the first step is alkylation by an allyl halide and the second step is alkylation by the electrophilic olefin (*50*). The reaction

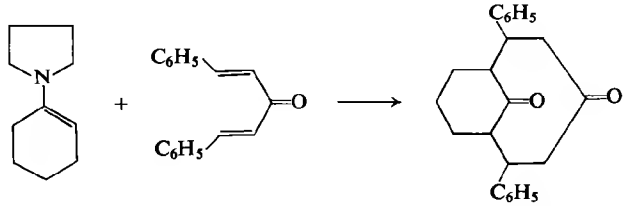


(**42**) (**34**) (**43**)

involves dimethyl bromomesconate (**42**) and 1-(N-pyrrolidino)cyclohexene (**34**) which, after hydrolysis, yields bicyclic ketodiester **43**.

The addition of *p*-quinone to enamines normally produces furan derivatives, especially when the enamine possesses a β hydrogen (see Section III.A). 1,2 Cycloaddition is claimed to take place to give a cyclobutane derivative when *p*-quinone and an enamine with no β hydrogens are allowed to react at low temperatures (*51*). However, little evidence is reported to verify this structural assignment, and the actual structure probably is a benzofuranol (*52*). Reaction of a dienamine (formed in situ) with *p*-quinone in the presence

of acetic acid results in two 1,4 cycloadditions to form a 2:1 dienamine–quinone carbocycle adduct (*53*). Another conjugated ketone, dibenzalacetone (**44**), adds to the pyrrolidine enamine of cyclohexanone to yield a bicyclo[5.3.1]undecane adduct **45** (*54*). N-Ethyl maleimide and N,N-dimethylaminoisobutyraldehyde add by 1,2 cycloaddition to give a cyclobutane derivative (*37*). Cyclopropenones also react with enamines to give carbocyclic products (*55,56*) (see Section II.B for further discussion of this).



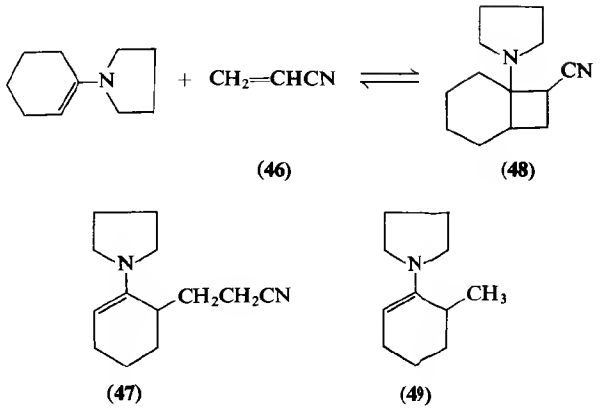
(**44**) (**45**)

3. *Conjugated with Nitrile, Nitro, or Sulfone Groups*

Olefins conjugated with electron-withdrawing groups other than a carbonyl group undergo reactions with enamines in a manner similar to the carbonyl-conjugated electrophilic alkenes described above. Namely, they condense with an enamine to form a zwitterion intermediate from which either 1,2 cycloaddition to form a cyclobutane ring or simple alkylation can take place.

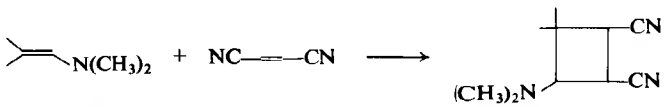
Such an electron-withdrawing group is the nitrile. Acrylonitrile (**46**) adds to enamines in a manner very similar to that of acrylate esters. 1,2 Cycloaddition of the unsaturated nitrile with the enamine is the initial step in almost all cases (*9*). The thermal stability of the cyclobutane product depends upon the absence or presence of a β hydrogen in the original enamine. Cyclobutane adducts derived from enamines without β hydrogens are thermally stable above room temperature and can be distilled. Those cyclobutane adducts obtained from enamines with β hydrogens are thermally unstable and will decompose upon distillation to give back starting materials and/or simple alkylated products. For example, Stork observed that acrylonitrile (**46**), when refluxed with 1-(N-pyrrolidino)cyclohexene in dioxane solvent, produced simple alkylated product **47** (*6*).

It was later noted that at low temperatures cyclobutane adduct **48** is formed from this reaction mixture, but as the temperature is increased, the adduct reverts back to starting material and also forms some of simple



(**46**) (**48**) (**47**) (**49**)

alkylation product **47** (*9*). The reaction between acrylonitrile (**46**) and 6-methyl-1-(N-pyrrolidino)cyclohexene (**49**) at room temperature produced an equilibrium mixture of cyclobutane adduct and starting materials, thus illustrating the steric sensitivity of the 1,2-cycloaddition reaction (*9*). On the other hand, when N,N-dimethylaminoisobutene (**10**), an enamine with no β hydrogens, is allowed to react with fumaronitrile (**50**) a thermally stable cyclobutane adduct (**51**) is formed in a 73% yield (*37*). Similar observations have been made by others (*13,20b,39*).



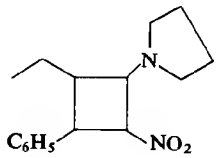
(**10**) (**50**) (**51**)

α-Chloroacrylonitrile undergoes 1,2 cycloaddition with aldehydic enamines to give the corresponding cyclobutane adducts (*49a*). However, when it is allowed to react with the enamines of cyclic ketones, quaternary chloride salts are formed by the 1,3 cycloaddition of the enamine to the electrophilic olefin.

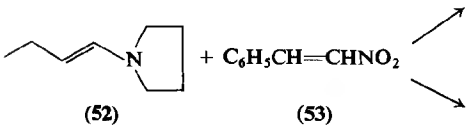
Nitroolefins also offer the possibilities of 1,2 cycloaddition (*37,57*) or simple alkylation (*57–59*) products when they are allowed to react with enamines. The reaction of nitroethylene with the morpholine enamine of cyclohexanone led primarily to a cyclobutane adduct in nonpolar solvents and to a simple alkylated product in polar solvents (*57*). These products are evidently formed from kinetically controlled reactions since they cannot be converted to the other product under the conditions in which the other

product was formed, and hence there is apparently no equilibrium set up between either of the products and the zwitterion intermediate.

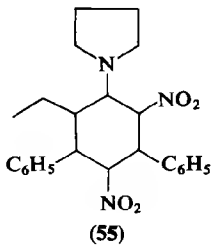
The reaction between the pyrrolidine enamine of butyraldehyde (**52**) and β-nitrostyrene (**53**) provides cyclobutane adduct **54** quantitatively in either petroleum ether or acetonitrile solvent, but in the more polar ethanol solvent a 2:1 condensation product occurred. The structure of the product was shown to be **55** (*57*).



(**54**)



(**52**) (**53**)



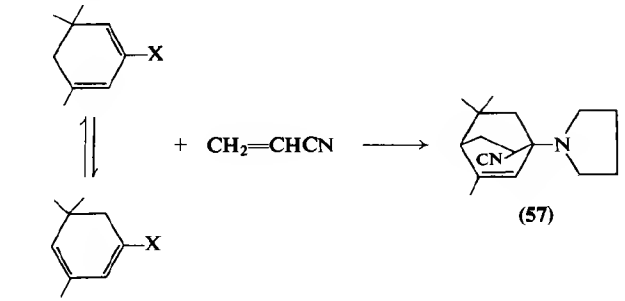
(**55**)

An unusual 1,4 heterocycloaddition has been reported to take place when an enamine is treated with 2-nitropropene in ether at 0°C to form an oxazine derivative (*59a*).

Methyl vinyl sulfone forms 1,2-cycloaddition adducts with aldehydic enamines, both with and without β hydrogens (*37*). Simple alkylation was reported to take place when phenyl vinyl sulfone was allowed to react with cyclohexanone enamines (*58,60*), but it has recently been shown that phenyl vinyl sulfone also forms cyclobutane adducts (*60a*).

Dienamine **56a** has been reported to undergo a 1,4 cycloaddition with acrylonitrile to form bicycloaminonitrile **57** in a 74% yield (*61*). A recent report has indicated that both possible 1,4-cycloaddition adducts are obtained from the reaction of acrylonitrile with a 1:1 equilibrium mixture of the linear- and cross-conjugated isomers of dienamine **56b** (*61a*).

Similar adducts are formed when the dienamine is allowed to react with methyl vinyl ketone and with methyl acrylate.



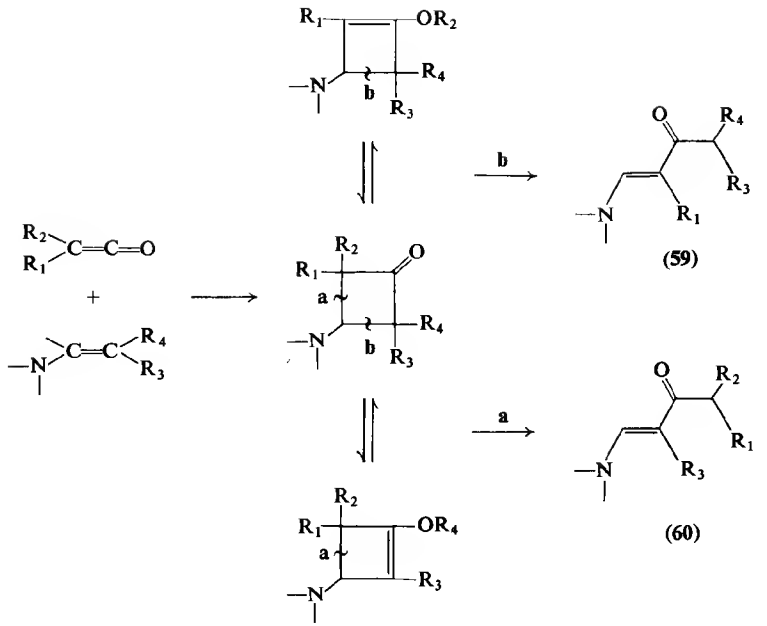
(**56a**): X = —N

(**56b**): X = —N O

4. *Cumulated with Carbonyl Group*

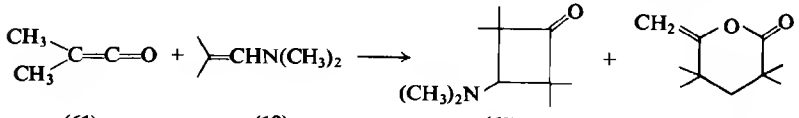
The treatment of enamines with acid halides which possess no α hydrogens results in the simple acylation of the enamine (*7,12,62–67*). If the acid halide possesses an α hydrogen, however, ketenes are produced in situ through base-catalyzed elimination of hydrogen chloride from the acid halide. The base catalyst for this reaction may be the enamine itself or some other base introduced into the reaction mixture such as triethylamine. However, if the ketene is produced in situ instead of externally, there still remains the possibility of a side reaction between the acid halide and the enamine other than the production of ketene (*67,84*).

The initial reaction between a ketene and an enamine is apparently a 1,2 cycloaddition to form an aminocyclobutanone adduct (**58**) (*68–76a*). This reaction probably occurs by way of an ionic zwitterion intermediate (*75*). The thermal stability of this adduct depends upon the nature of substituents R_1, R_2, R_3, and R_4. The enolic forms of **58** can exist only if R_2 and/or R_4 are hydrogens. If the enamine involved in the reaction is an aldehydic enamine with no β hydrogens and the ketene involved is disubstituted (i.e., R_1, R_2, R_3, and R_4 are not hydrogens), then the cyclobutanone adduct is thermally stable. For example, the reaction of dimethylketene (**61**) with N,N-dimethylaminoisobutene (**10**) in isopropyl acetate



(58) (59) (60)

solvent produces 3-(N,N-dimethylamino)-2,2,4,4-tetramethylcyclobutanone (**62**) in a 64% yield, a product which can be distilled with no decomposition (*75*). Some 2:1 and 3:1 dimethylketene–enamine adducts are also formed during this reaction. If acetonitrile is used as solvent, then larger quantities of the 2:1 and 3:1 adducts are formed at the expense of the 1:1

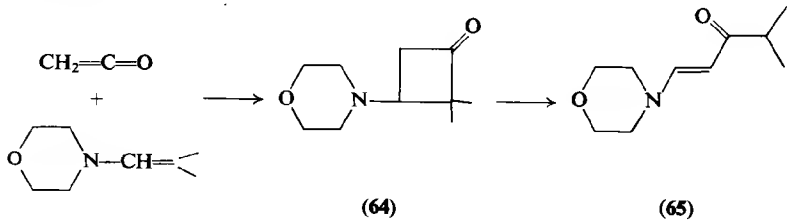


(61) (10) (62) (63)

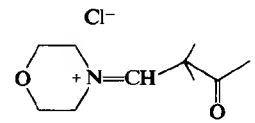
adduct (*75*). The 2:1 adduct was identified as δ lactone **63** (*77*), which undoubtedly is formed by the further addition of a dimethylketene molecule to the initially formed zwitterion intermediate. The structure of this product is analogous to the cyclic trimer of dimethylketene (*78*).

The reaction between an aldehydic enamine with no β hydrogens and ketene yields a cyclobutanone adduct which is not thermally stable (R_3 and $R_4 \neq H$, $R_1 = R_2 = H$) (*67,70,72*). Thermal decomposition gives just one

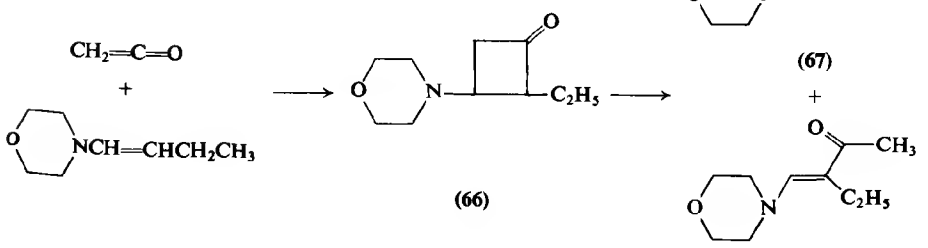
product by way of pathway **b**. This is illustrated by treating 1-(N-morpholino)isobutylene with ketene to yield adduct **64**, which decomposes upon heating to vinyl amide **65** (*70,73*). When this enamine is allowed to react with acetyl chloride alone, only simple acylation of the enamine takes place to form hydrochloride salt **65a** (*67*). Cyclobutane adduct **64** was shown not to cleave and form **65a** under these reaction conditions and hence is not a precursor in this reaction (*67*). Apparently simple acylation by the acid halide occurs more rapidly than ketene formation with only the weakly basic morpholine enamine acting as base catalyst (*84*). Aldehydic enamines with β hydrogens, such as 1-(N-morpholino)butene, undergo 1,2 cycloaddition with ketene to form a very unstable cyclobutane adduct ($R_2 = R_4 = H$), in this case adduct **66**. This adduct rapidly changes into a mixture of vinyl amides via pathways **b** and **a**, in this case vinyl amides **67** and **68** in a 4:1 ratio (*73*).



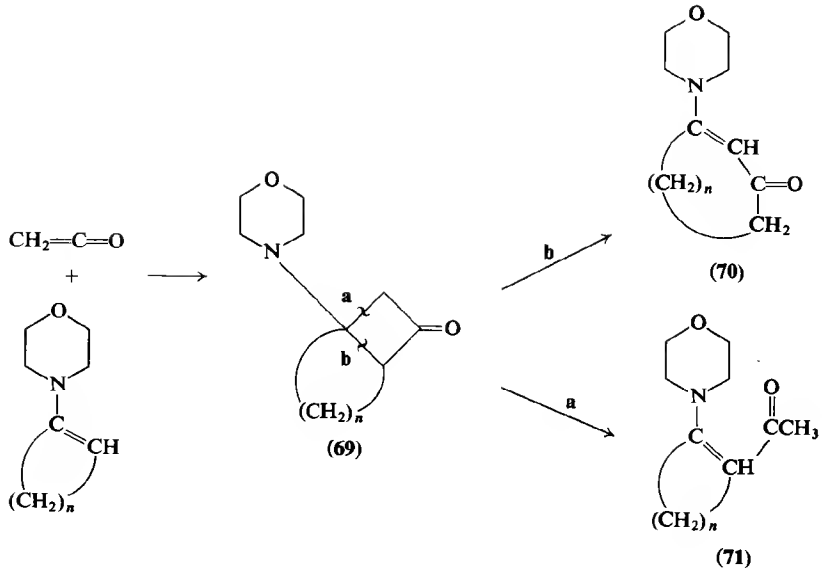
(64) (65)



(65a)



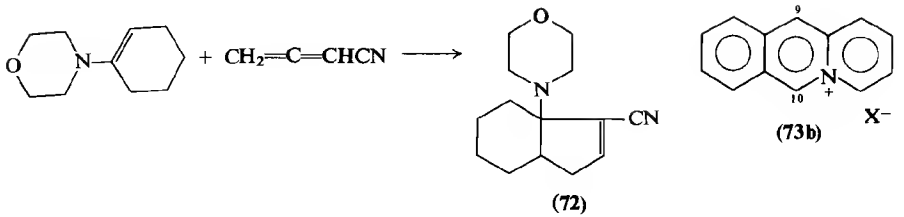
(66) (67) (68)

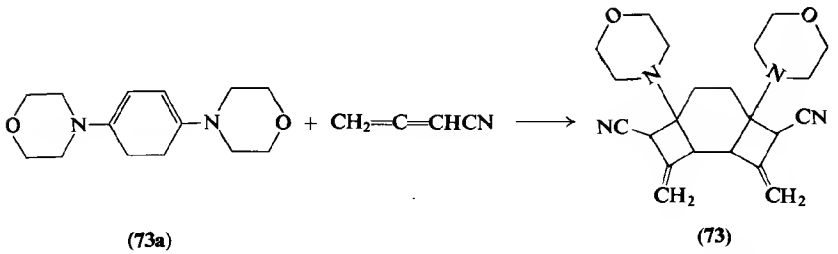


Enamines derived from cycloalkanones add to ketene to produce first a cyclobutanone adduct **69** (*69,70*) followed by cleavage of the cyclobutane ring at **a** or **b**. The point of cleavage of the cyclobutane ring depends upon the ring size of the original cycloalkanone. For adducts from five- and six-membered cycloalkanone enamines ($n = 3$ and 4), decomposition takes place by pathway **a** (*69,70,72,73,79–88b*). The adduct from the nine-membered ring enamine ($n = 7$) is produced in very poor yields and decomposition follows both path **a** and path **b** (*84,88b*). As the enamine ring size increases from ten-membered through fifteen-membered (*83,84,84a,88,88a, 88b*), the cyclobutane ring cleavage follows path **b** and the amount of product increases. Treatment of enamines obtained from ketones with excess ketene produces 2H-pyran-2-ones (*73*) (see Section III.A).

5. *Others*

Cyanoallene, when treated with the morpholine enamine of cyclohexanone, undergoes a 1,3-cycloaddition reaction to form **72** (*89*). The reaction between cyanoallene and diendiamine **73a** produces di-1,2-cycloaddition adduct **73** (*89*). The 4a-azonioanthracene ion (**73b**) readily undergoes a 1,4-cycloaddition reaction with nucleophilic dienophiles such as enamines (*89a*). The cycloaddition is stereoselective so that the α- and

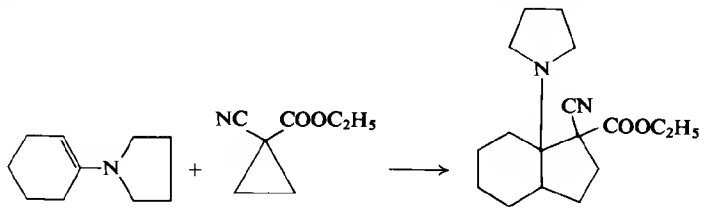




β-carbon atoms of the enamine add to the 10 and 9 positions respectively, of the 4a-azonioanthracene ion.

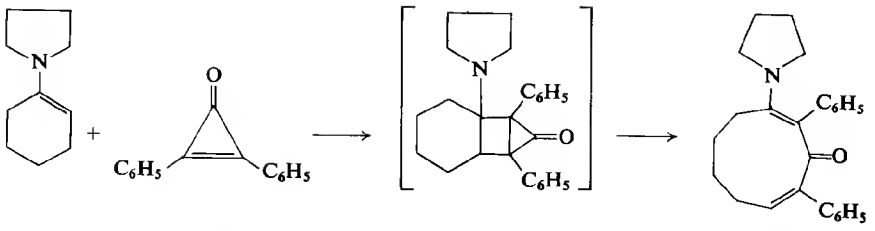
B. Electrophilic Cyclopropanes and Cyclopropenes

The similarity between the reactions of alkenes and cyclopropanes is further demonstrated by the reactions of electrophilic cyclopropanes and cyclopropenes with enamines. Cyclopropylcyanoester **74**, when treated with the pyrrolidine enamine of cyclohexanone, undergoes what would be a 1,2 cycloaddition in the analogous alkene case, but is actually a 1,3 cycloaddition here, to form adduct **75** (*90*). A similar reaction between the

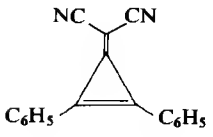


heterocyclic three-membered ring, N-carbethoxyaziridine, and this enamine to form a heterocyclic product has also been observed (*91*) (see Section III.C).

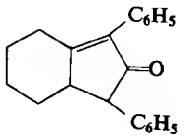
Diphenylcyclopropenone (**76**) undergoes a true 1,2 cycloaddition with alicyclic enamines followed by the breaking of sigma bonds in the intermediate (*55,56*). For example, when diphenylcyclopropenone (**76**) is



(76) (77)



(79)



(78)

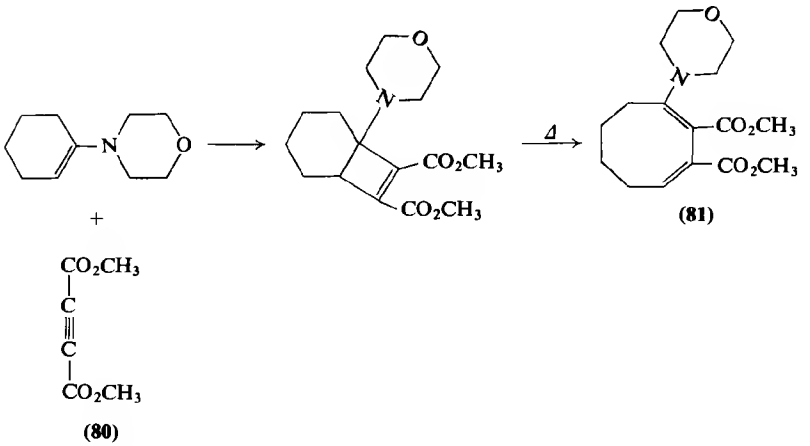
allowed to react with the pyrrolidine enamine of cyclohexanone, both nonanone **77** and bicyclic ketones **78** are produced, depending upon which bonds are broken in the intermediate (*56*). The reaction between diphenylcyclopropenone and an acyclic dienamine results in an initial 1,4 cycloaddition with diphenylcyclopropenone, the dienophile, followed by the breaking of a sigma bond to form a tropone (*56*). However, a similar reaction between an acyclic dienamine and triafulvene **79** causes an initial 1,2 cycloaddition to the 3,4 double bond of the dienamine followed by sigma bond breaking to form an acyclic product (*92*). Treatment of either **76** or **79** with acyclic enamines yields acyclic enaminoketone products (*56,92*).

C. Electrophilic Alkynes

Terminal alkynes with no electron-withdrawing group next to the acetylenic linkage when treated with enamines merely add across the double bonds of the enamines (*93*). But electrophilic alkynes (those with an electron-withdrawing group next to the acetylenic linkage) undergo cycloaddition reactions with enamines.

Dimethyl acetylenedicarboxylate (**80**) undergoes initial 1,2 cycloaddition with acyclic enamines to form cyclobutene intermediates which immediately decompose into acyclic dienaminodiesters (*94,95*). When an acyclic *vic*-enediamine is used instead of a simple acyclic enamine, a dienediaminodiester is produced via a cyclobutene intermediate (*95a*). A cyclization reaction of dimethyl acetylenedicarboxylate with an acyclic enaminoketone

was reported to result in the formation of a phthalate ester (*96,97*). Alicyclic enamines, when treated with dimethyl acetylenedicarboxylate, yield ring enlargement products two members larger than the original via cyclobutene adduct intermediates (*95,97,98*). Six-membered ring enamines produce stable cyclobutene adducts with dimethyl acetylenedicarboxylate, which then decompose into ring enlargement products upon heating (*95,97*). This is illustrated by the reaction of the morpholine enamine of cyclohexanone with dimethyl acetylenedicarboxylate (**80**) to form, after heating, cyclooctadiene **81** (*97*). This enamine undergoes a similar ring enlargement when it is allowed to react with methyl phenylpropiolate (*99*). In some cases the dienamine ring expansion product undergoes a 1,4

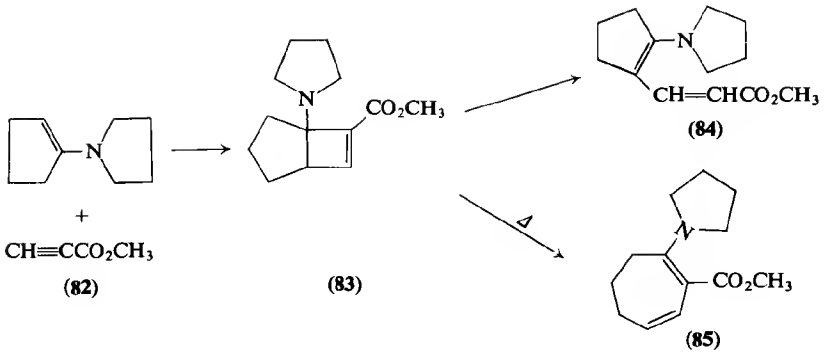


(81)

(80)

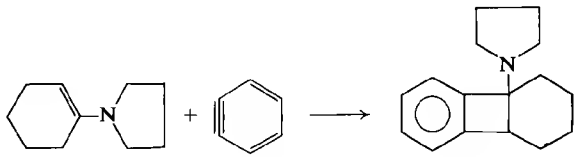
cycloaddition with a second molecule of dimethyl acetylenedicarboxylate (*99*).

The reaction of methyl propiolate (**82**) with acyclic enamines produces acyclic dienamines (*100*), as was the case with dimethyl acetylenedicarboxylate, and the treatment of the pyrrolidine enamines of cycloheptanone, cyclooctanone, cycloundecanone, and cyclododecanone with methyl propiolate results in ring enlargement products (*100,101*). When the enamines of cyclohexanone are allowed to react with methyl propiolate, rather anomalous products are formed (*100*). The pyrrolidine enamine of cyclopentanone forms stable 1,2-cycloaddition adduct **83** with methyl propiolate (**82**). Adduct **83** rearranges to the simple alkylation product **84** upon standing at room temperature, and heating **83** to about 90° causes ring expansion to **85** (*97,100*).



(82) (83) (84) (85)

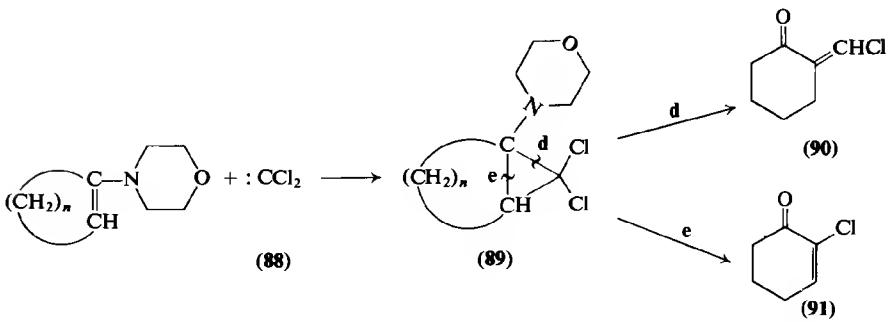
The reaction of an alicyclic enamine with benzyne intermediate yields simple arylation products and/or 1,2-cycloaddition products, depending upon the reaction conditions (*102*). This is illustrated by the reaction of 1-(N-pyrrolidino)cyclohexene with benzyne (**86**) (obtained from fluorobenzene and butyl lithium or *o*-bromofluorobenzene and lithium amalgam), which produces benzocyclobutene **87** (*102*).



(86) (87)

D. Divalent Carbon

Addition of dichlorocarbene (**88**) to the enamine of cyclohexanone gives a relatively stable adduct **89** ($n = 4$) (*103–105*). Hydrolysis of this adduct



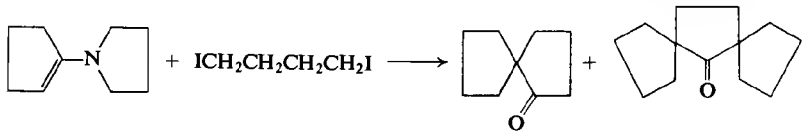
(88) (89) (90) (91)

causes cleavage at **d** and formation of ketone **90** (*105*). When the enamine of cyclopentanone is treated with dichlorocarbene, the adduct (**89**, $n = 3$) is unstable and cleavage at **e** occurs to form ring expanded product **91** (*104, 105*). Acyclic enamines also form unstable adducts with dichlorocarbene, which are readily hydrolyzed through an **e**-type cleavage to produce α-chloro-α,β-unsaturated aldehydes (*106*). Addition of methylene to enamines to form aminocyclopropanes has been carried out by using bis(iodomethyl)zinc (*106a*), methylene iodide with zinc–copper couple (*106b*), and diazomethane in the presence of cuprous (*106c*) as the sources of methylene. The use of diazomethane with cuprous chloride gives the best yields. Diphenylcarbene, produced by the bis(acetylacetonato)-copper(II)-catalyzed decomposition of diphenyldiazomethane, also reacts with enamines to form cyclopropylamines (*106d,106e*).

E. Miscellaneous

Stereochemical positioning of a functional group, relative to a separate enamine moiety in the same molecule, can be done in such a manner that a simple intramolecular alkylation or acylation will cause cyclization. Such intramolecular cycloalkylations with alkyl halides have been reported (*107,108*). Intramolecular cycloacylations of enamines with esters (*109, 110,110a*) and with nitriles (*110a,111,111a*) have also been observed.

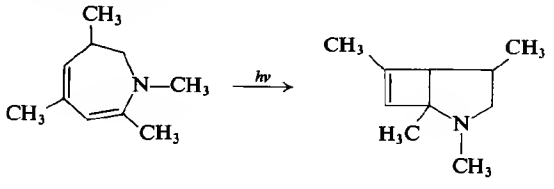
Bifunctional molecules undergo intermolecular cyclizations with enamines through simple alkylations (*112–114*) and acylations (*115*). For example, the reaction between 1-(N-pyrrolidino)cyclopentene and 1,4-diiodobutane produces, after hydrolysis, ketospirans **92** and **93** (*113*).



(92) (93)

Enamines containing one β-hydrogen atom react with the lactone dimer of dimethylketene to form aminocyclohexanediones (*116*). Polycondensation of acetone diethyl ketal takes place by treating it with morpholine and a catalytic amount of *p*-toluenesulfonic acid while distilling off the ethanol formed (*117–119*). The resulting spiran, bicyclo, and cyclooctadienone products differ from the known polycondensation products of acetone, and hence their formation probably involves enamine intermediates (*119*).

Irradiation of dienamine **94** for 3 days results in the formation of **95** through a 1,4 cycloaddition (*120*).



(94) **(95)**

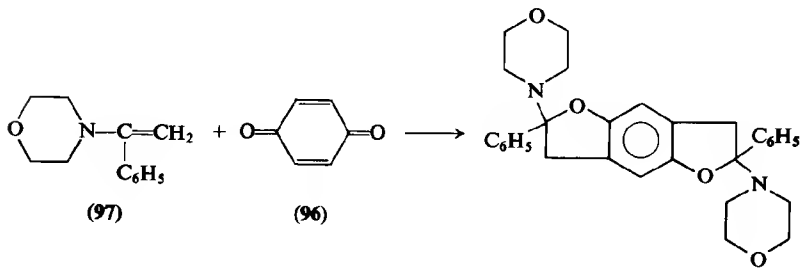
It has been reported that perfluoroisobutylene and perfluorocyclobutene undergo 1,2 cycloaddition with 1-(N-morpholino)isobutylene in ether at room temperature to give the corresponding perfluorocyclobutane derivatives (*120a*). Enamines of cyclic ketones produce only simple alkylation products when treated with these perfluoroolefins.

III. Heterocycloadditions

A. Oxygen Heteroatom

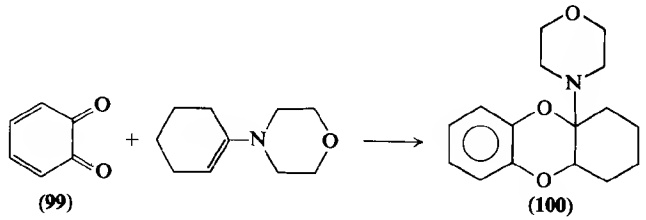
Dihydropyrans have been produced by the 1,3 cycloaddition of methyl vinyl ketone (*11*) or acrolein (*29–31*) with enamines (see Section II.A.2). δ-Lactones have been formed as a side product in the reaction of dimethyl ketene with enamines (*77*), and as the primary products in the reaction of excess ketene with enamines derived from ketones (*73*) (see Section II.A.4).

p-Quinone (**96**) undergoes 1,3 cycloaddition, di-1,3 cycloaddition, or both when it is treated with enamines to form benzofuranols (*52,121,122,122a*) and/or benzodifurans (*123,124*). For example, when 1-(N-morpholine)-1-phenylethene (**97**) is allowed to react with *p*-quinone (**96**), benzodifuran **98** is formed (*124*).



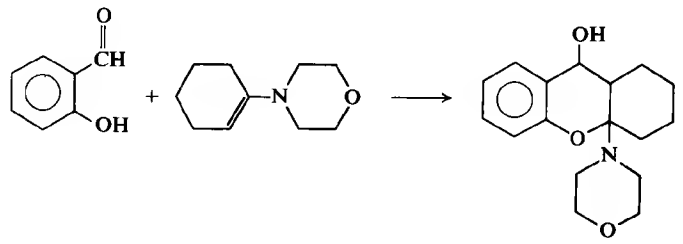
(97) **(96)** **(98)**

Adduct **100** is formed from the 1,4 cycloaddition of *o*-quinone (**99**) with the morpholine enamine of cyclohexanone (*125*). Treatment of styrene oxide with cyclic enamines at elevated temperatures (about 230°C) produces O,N-ketals possessing a furan nucleus (*125a*).



(99) **(100)**

The synthesis of a large number of γ-pyrones and γ-pyranols from enamines has been brought about through the use of a wide variety of bifunctional molecules. These molecules include phenolic aldehydes (*126,127*), phenolic Mannich bases (*128*), ketal esters (*129*), and diketene (*130–132*). All of these molecules have an electrophilic carbonyl group and a nucleophilic oxygen center in relative 1,4 positions. This is illustrated by the reaction between salicylaldehyde (**101**) and the morpholine enamine of cyclohexanone to give pyranol **102** in a quantitative yield (*127*).

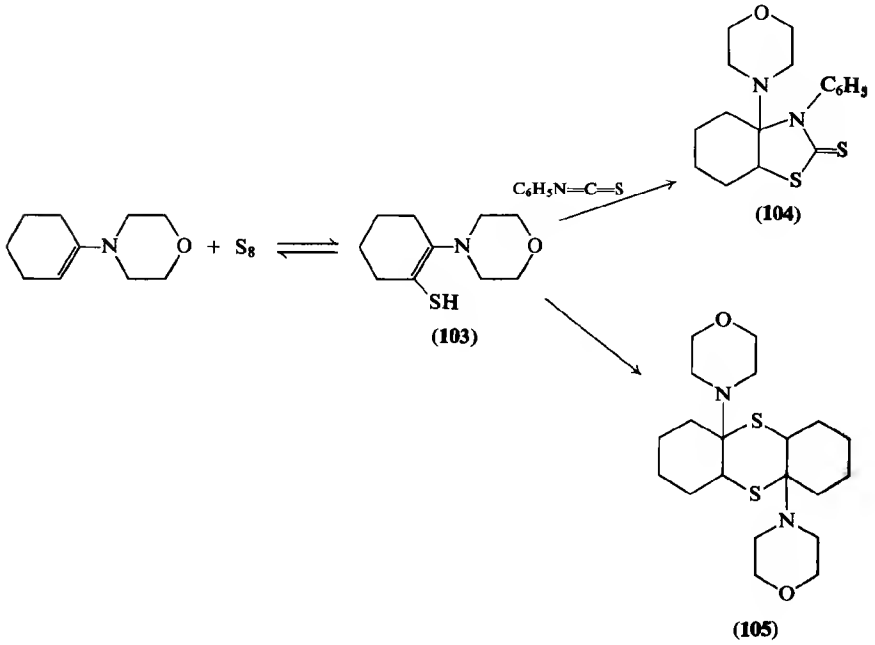


(101) **(102)**

A cyclic peroxide is obtained when an enaminoester is treated with hydrogen peroxide (*133*). The dye-sensitized photooxygenation of enamines, resulting in the ultimate formation of a ketone or aldehyde and an amide by cleavage of the double bond, probably involves a cyclic peroxide intermediate (*133a–133c*). Such an intermediate could form by the 1,2-cycloaddition of a singlet oxygen molecule to the enamine's carbon–carbon double bond.

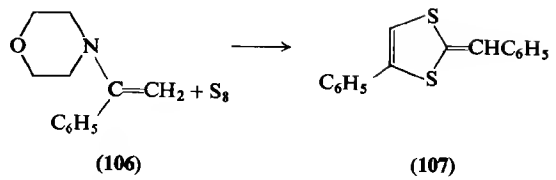
B. Sulfur Heteroatom

Elemental sulfur undergoes nucleophilic attack by amines at low temperatures. Therefore the conjugate β position of an enamine is sufficiently nucleophilic to attack elemental sulfur and yield thiolated intermediate **103**. When **103** is treated when phenyl isothiocyanate, the cyclic adduct **104**



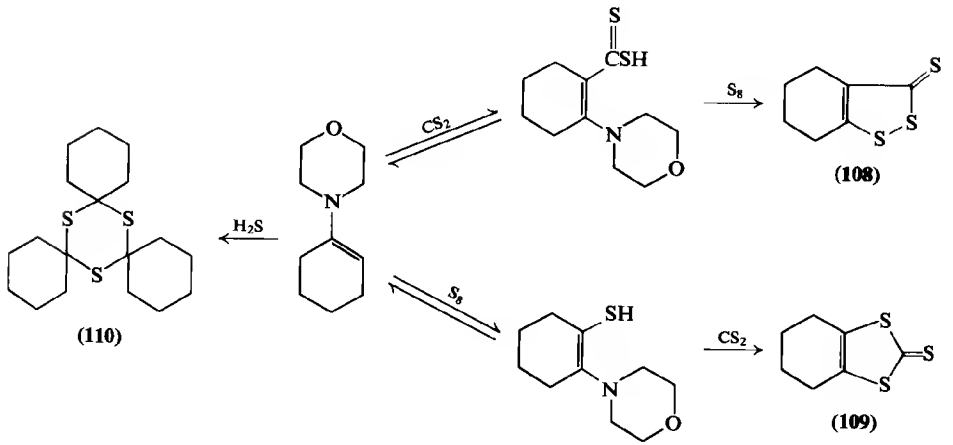
is formed (*134*). In a similar manner **103** produces an aminothiazole when treated with cyanamide (*135*). A thiazolidone is formed when **103** is treated with an isocyanate (*136*) (see Section III.C). Refluxing the morpholine enamine of cyclohexanone and elemental sulfur in benzene solvent results in the formation of hydrogenated thianthrene **105** (*137*).

Many acyclic enamines form thioamides when they are allowed to react with elemental sulfur at room temperature in dimethylformamide solvent (*138*). They also produce cyclic 1,3-dithiole by-products, which become main products at higher temperatures (*135*). For example, the reaction of 1-(N-morpholino)-1-phenylethene (**106**) and sulfur in dimethylformamide solvent yields 1,3-dithiole **107**.



(106) (107)

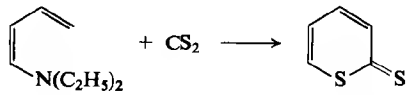
Carbon disulfide can act as an electrophilic agent with enamines at room temperature. Therefore, treatment of an enamine with both elemental sulfur and carbon disulfide in a polar solvent can result in the formation of a 3H-1,2-dithiole-3-thione (such as **108**) and/or a 2H-1,3-dithiole-2-thione (such as **109**) (*135,139,140*). These products are the result of competing



reaction paths, each of which is initiated by a different electrophilic agent, namely, sulfur and carbon disulfide. All aliphatic and many aromatic enamines give 3H-1,2-dithiole-3-thiones as the exclusive products when treated with sulfur and carbon disulfide. Some aromatic enamines, however, yield 2H-1,3-dithiole-2-thione products (*135*). A 1,3-dithiolethione product is also obtained by allowing an enamine to react with thiuram disulfides and hydrogen sulfide (*135,141*). Treatment of the morpholine enamine of cyclohexanone with hydrogen sulfide alone gives cyclic product **112** (*142*).

A by-product of the reaction between an enamine, elemental sulfur, and carbon disulfide is an α-dithiopyrone. This by-product is the result of the condensation of two enamine molecules with one carbon disulfide molecule. In the case of aldehydic enamines, the reaction probably proceeds through

a carbon disulfide catalyzed enamine condensation to form a dienamine. Carbon disulfide then adds to the dienamine, yielding an α-thiopyrone. This last step is illustrated by the reaction between dienamine **111** and

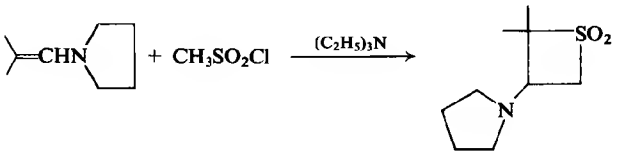


(111) **(112)**

carbon disulfide to produce α-dithiopyrone **112** (*135*). Enamines of aliphatic methyl ketones and aromatic methyl ketones apparently add carbon disulfide first and then condense with a second enamine molecule to give α-dithiopyrones without passing through the dienamine stage. Enamines of cyclic ketones do not yield α-dithiopyrone products when treated with carbon disulfide.

The formation of α-dithiopyrone by-products during the reaction of an enamine with elemental sulfur and carbon disulfide is enhanced by one or a combination of the following: the carbon disulfide is allowed to stand for a long period of time with the enamine in the absence of sulfur, a high reaction temperature, and the use of a relatively nonpolar solvent (*135*).

Sulfenes ($R_2C=SO_2$) are the sulphonyl analogs of ketene, and they can readily be generated by various means, including treatment of sulfonyl chlorides with bases such as triethylamine and treatment of diazomethanes with sulfur dioxide (*143*). It has been observed that sulfene (usually generated in situ from methanesulfonyl chloride and triethylamine) undergoes 1,2 cycloaddition with enamines to form a β-aminothietane dioxide regardless of whether a β hydrogen is present in the original enamine or not (*144–152*).



(113) **(114)**

This is illustrated by the reaction of enamine **113** with sulfene to produce adduct **114** in an 80% yield (*146*). The product **114** was also observed in an 18% yield from the reaction of diazomethane, sulfur dioxide, and enamine **113** (*153*). It was demonstrated that this cyclization reaction must involve sulfene adding to the enamine directly and not acylation of the enamine by

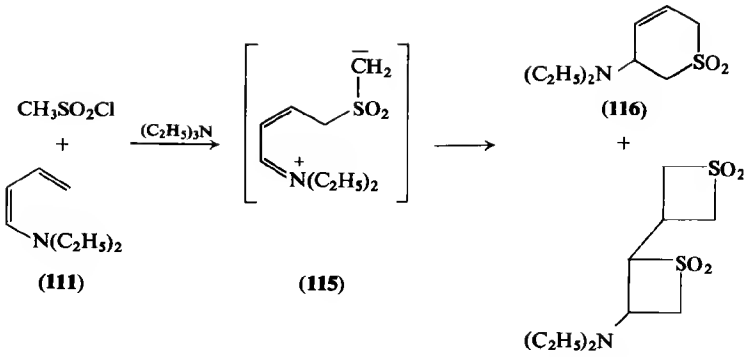
methanesulfonyl chloride followed by cyclization (*145,148,153*). However, in some reactions acylation products were found along with cyclization products (*145,148,152*), in others the acylation product was almost the exclusive product (*147,154*). It is not entirely clear whether the simple acylation product forms by direct acylation of the enamine by a sulfonyl chloride such as is the case with phenyl sulfonyl chloride, where no sulfene intermediate is possible (*155*), or whether a cyclic sulfone or at least a zwitterion intermediate arising from sulfene addition is involved in the simple acylation. The latter appears to be a strong possibility (*154*).

The cycloaddition of sulfene to bicyclo[2.2.1]heptyl enamines is stereospecific, addition coming from the exo side (*156*). However, the steric preference of *cis* and *trans* isomers relative to the four-membered ring generated does not seem as strong, at least in the case of the addition of chlorosulfene ($ClCH=SO_2$) to bicyclic enamines, where a mixture of stereoisomers is obtained (*157*).

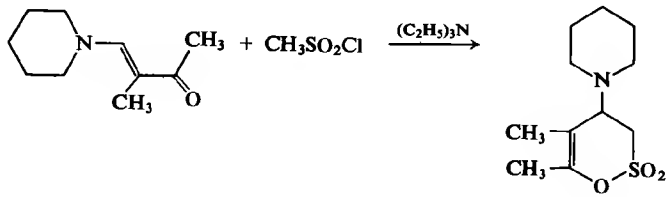
The mechanism of the cycloaddition of sulfenes to enamines does not involve a concerted process in many if not all cases, but rather a two-step process in which a zwitterion is the initially formed intermediate (*158,159*).

Dienamines undergo 1,4 cycloaddition with sulfenes as well as 1,2 cycloaddition. For example, 1-(N,N-diethylamino)butadiene (**111**), when treated with sulfene (generated from methanesulfonyl chloride and triethylamine), produces 1,4 cycloadduct **116** in an 18% yield and di-1,2-cycloadduct **117** in a 60% yield (*160*). Cycloadduct **116** was shown not to be the precursor for **117** by treating **116** with excess sulfene and recovering the starting material unchanged (*160*). This reaction probably takes place by way of zwitterion **115**, which can close in either a 1,4 or 3,4 manner to form cycloadducts **116** and **118**, respectively. The 3,4 cycloaddition would then be followed by a 1,2 cycloaddition of a second mole of sulfene to form **117**. Cycloadduct **117** must form in the 3,4 cycloaddition followed by a 1,2-cycloaddition sequence rather than the reverse sequence since sulfenes undergo cycloaddition only in the presence of an electron-rich olefinic center (*159*). Such a center is present as an enamine in **118**, but it is not present in **119**.

1,3-bis(Dimethylamino)-1-alkenes undergo similar reactions with sulfenes because of the possibility of the elimination of the elements of dimethylamine to form a dienamine (*159,161*). These 1,3-diaminoalkenes, when treated with sulfenes, also yield other products which are formed primarily because of the presence of a nonenamine tertiary nitrogen at C-3, which can compete with the neighboring enamine system for the electrophilic sulfene (*158,159,162*).



Enaminoketones undergo 1,4 cycloadditions with sulfene (*162a*). This is illustrated by the reaction of enamine **120** with sulfene to form sulfone **121** in an 80% yield (*162,163*).



(120) **(121)**

α,β-Unsaturated sulfenes, obtained by treatment of allyl sulfonyl chlorides with triethylamine, have been observed to undergo only 1,2 cycloaddition with enamines (*164*). Simple sulfonylation products also resulted from these reactions.

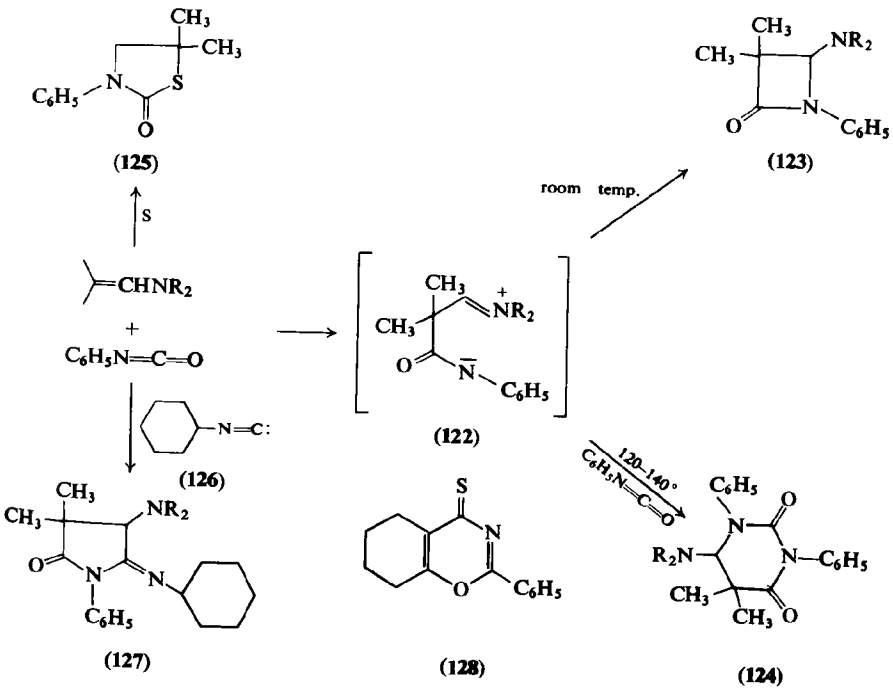
Disulfenes react with 2 moles of enamine to produce a double 1,2-cycloaddition adduct (*164a*).

Stable sulfenes have been isolated by treating methanesulfonyl chloride. with triethylamine or trimethylamine in acetonitrile solvent at −40°C (*165,166*). These stable sulfenes undergo 1,2 cycloaddition with enamines to form the expected thietanes (trimethylenesulfones).

C. Nitrogen Heteroatom

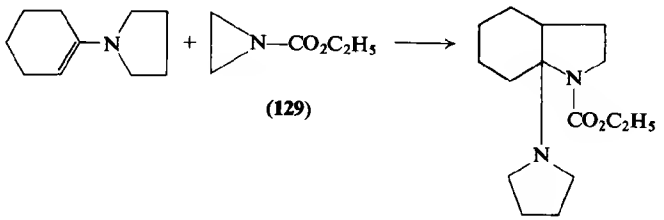
1. *1,2 and 1,4 Cycloadditions*

Treatment of enamines possessing β hydrogens with isocyanates or thioisocyanates results in the formation of the corresponding carboxamides or thiocarboxamides (*167–171*). The reaction of an enamine possessing no β hydrogens with phenylisocyanate at room temperature produces β-lactam **123** by 1,2 cycloaddition (*172,173*), probably via zwitterion intermediate **122**. At higher temperatures a second mole of phenylisocyanate adds to **122**, yielding aminohydrouracil **124** (*174*). A similar reaction is observed with phenylisothiocyanate (*174a*). When another reagent is present such as



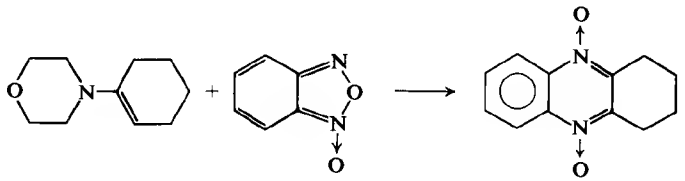
sulfur (*136*) or cyclohexylisonitrile (**126**) (*175*), cyclization to form five-membered rings takes place, in these cases 1,3-thiazolidin-2-one (**125**) and pyrrolidone (**127**), respectively. Treatment of the morpholine enamine of cyclohexanone with benzoylisothiocyanate produces cycloadduct **128** (*176*).

A pseudo 1,2 cycloaddition (actually a 1,3 cycloaddition, but may be considered a 1,2 type if a three-membered ring is considered analogous to an alkene) is observed when the pyrrolidine enamine of cyclohexanone is allowed to react with N-carbethoxyaziridine (**129**) to produce octahydroindole **130** (*91*). Octahydroindoles and pyrrolidines can also be produced through the intramolecular alkylation of the enamines of certain haloketourethanes (*176a*).



(129) (130)

The reaction of isobenzofuroxan (**131**) with the morpholine enamine of cyclohexanone results in a 1,4 cycloaddition to form quinoxaline-di-N-oxide **132** (*177*). Quinone dibenzenesulfonimide has been found to undergo



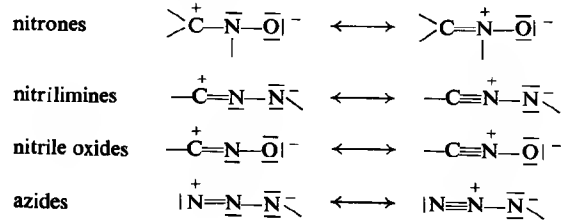
(131) (132)

1,4 cycloaddition with enamines in a manner similar to that of *p*-quinone (*102*) (see Section II.A). A 1,4 cycloaddition due to difunctionality has been observed in a series of reactions between 3-bromopropylamine hydrobromide and various enamines to form tetrahydropyridines (*178*). α-Cyanocinnamide produces a 1,4-cycloaddition adduct when it is treated with the pyrrolidine or morpholine enamine of cyclopentanone or cyclohexanone (*178a*). An oxazine derivative is formed by the 1,4 cycloaddition of 2-nitropropene to an enamine (*59a*).

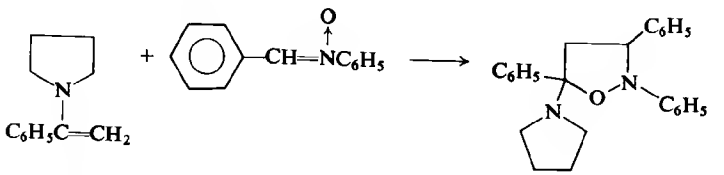
The photocyclization of N-aryl enamines derived from cyclic or acyclic ketones proceeds under mild conditions to produce 2,3-dihydroindole derivatives (*178b*). The stereochemistry of the products is predominantly *trans*, which follows from a photochemical electrocyclic process which should take place in a conrotatory manner (*178c,178d*). However, the presence of some *cis* products is not as easily explained.

2. *1,3-Dipolar Cycloadditions*

1,3 Cycloaddition across the double bond of an enamine to form an uncharged five-membered ring (except in the case of cyclopropane ring cleavage and addition) involves a dipolar reactant described by zwitterionic octet structures (*178e,178f*). Several of these reactions have been observed in which an enamine acts as the dipolarophile. The types of dipolar reactants which have been reported to undergo this type of 1,3 cycloaddition with dipolarophilic enamines are listed below.



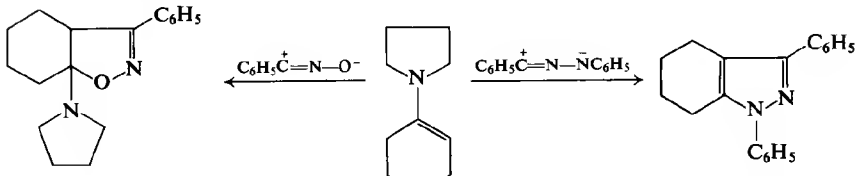
The cycloaddition of nitrones to enamines results in the formation of an isoxazolidine (*179,180*). The reaction of 1-(N-pyrrolidino)-1-phenylethylene (**133**) with nitrone **134** producing isoxazolidine **135** illustrates this type of cycloaddition (*180*).



(133) (134) (135)

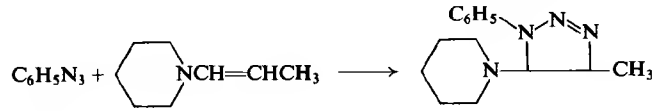
Nitrilimines can be produced by treating halogenated hydrazones with a base such as triethylamine. Thesc nitrilimines undergo 1,3 cycloaddition with enamines to form pyrazoles (*181–183*). This is shown by the reaction of the pyrrolidine enamine of cyclohexanone with diphenylnitrilimine to

form diphenyltetrahydroisoindazole (**136**) (*182*). Treatment of halohydroxamic acids with a base yields nitrile oxides, which in turn add to the dipolarophilic enamines to produce isoxazoles (*182,184,185*). Therefore benzonitrile oxide adds to the pyrrolidine enamine of cyclohexanone to yield aminodihydroisoxazole **137** (*182*). A dioxazole adduct is formed when 1,2-bis(N,N-diethylamino)ethylene is allowed to react with terephthalonitrile oxide (*95a*).



(137) (136)

Azides can use enamines as dipolarophiles for 1,3 cycloadditions to form triazolines. These azides can be formate ester azides (*186*), phenyl azides (*187–195*), arylsulfonyl azides (*191–193,196*), or benzoylazides (*197,198*). For example, the reaction between phenyl azide (**138**) and the piperidine enamine of propionaldehyde (**139**) gives 1-phenyl-4-methyl-5-(1-piperidino)-4,5-dihydro-1,2,3-triazole (**140**), exclusively, in a 53% yield (*190*). None of the isomeric 1-phenyl-5-methyl product was formed. This indicates that the

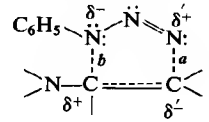


(138) (139) (140)

products formed from this reaction are the results of electronic control (*190*). The negative end of the azide dipole (the phenyl-substituted nitrogen) is directed to the β position of the enamine.

The mechanism of the cycloaddition of phenyl azide to norbornene has been shown to involve a concerted mechanism with a charge imbalance in the transition state (*199*). In a similar manner the cycloaddition of phenyl azide to enamines apparently proceeds by a concerted mechanism (*194, 194a*). This is shown by a rather large negative entropy of activation (−36 entropy units for 1-(N-morpholino)cyclopentene in benzene solvent at 25°C), indicative of a highly ordered transition state. Varying solvents from those of small dielectric constants to those of large dielectric constants has

only a small effect on the relative rates of the cycloaddition reaction. This also supports a concerted reaction mechanism. However, a very large positive Hammett ρ value of +2.5 for 1-(N-pyrrolidino)cyclohexene in benzene solvent at 25°C seems to militate against a concerted mechanism (*194*). These results can be correlated by describing the mechanism as



(141)

concerted with formation of transition state **141** and the formation of bond **a** being further developed than the formation of bond **b**, that is, $\delta-$ or $\delta+$ is greater than $\delta'-$ or $\delta'+$. This discrepancy in the extent of bond formation between **a** and **b** is greater with enamines as dipolarophiles than with unsubstituted olefins as dipolarophiles (*194*).

The reaction of cyanogen azide with enamines of cyclic ketones to yield a cyanoamidine with one less member in the carbocyclic ring represents a potentially valuable method of ring contraction under mild conditions (*199a*). The reaction probably proceeds first by 1,3 cycloaddition of the azide to the enamine followed by rearrangement and elimination of a molecule of nitrogen.

IV. Cycloadditions of Vinyl Ethers

Vinyl ethers undergo many cycloaddition reactions similar to those which take place with enamines. In general, however, these cycloaddition reactions with vinyl ethers take place less readily than those with enamines. These reactions include cycloaddition of vinyl ethers with ketene (*200–205*), phenyl isocyanate (*206*), sulfene (*207,208*), methyl acrylate (*209*), diethyl acetylenedicarboxylate (*210*), and diphenylnitrilimine (*183*).

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7

HETEROCYCLIC ENAMINES

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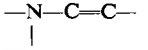
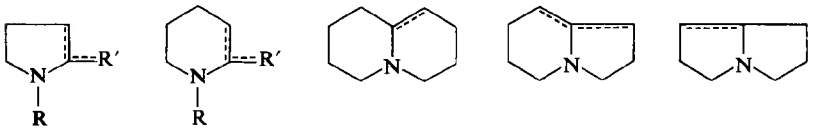
I. Introduction

As "heterocyclic enamines" we designate compounds containing an enamine grouping



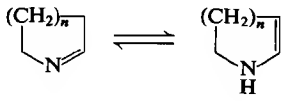
in the molecule in which all three atoms are a part of a heterocyclic system (*1*). Typical behavior of enamines has been mainly observed for

compounds possessing a tertiary nitrogen atom (*2*). In this group are included variously substituted dehydroderivatives of pyrrolidine (pyrrolines) (**1**), piperidine (piperideines) (**2**), rarely the derivatives of dehydro-1-azacycloalkanes with more than six-membered rings, and finally compounds containing some of these basic skeletons: enamines of quinolizidine (**3**), indolizidine (**4**), pyrrolizidine (**5**), and their benzoderivatives, which occur in a large number of alkaloids.



(1) (2) (3) (4) (5)

Analogous compounds with a secondary amino group (α,β-unsaturated secondary amines) can, in principle, exist in either the form of imines (**6**) or the tautomeric form of enamines (**7**). As they practically occur and react in the former structure, it is more convenient to use the group designation "imines."



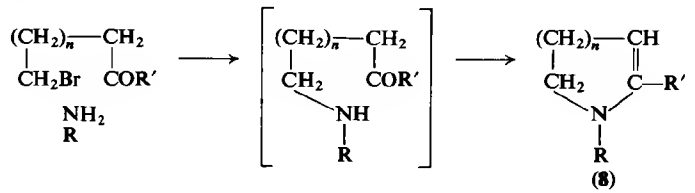
(6) (7)

II. Preparation of Heterocyclic Enamines

A. Condensation Reactions

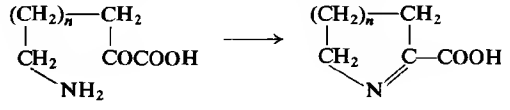
1. *Preparation of Heterocyclic Enamines from γ- and δ-Amino Ketones*

2-Alkyl-Δ^1-pyrrolines (**8**, $n = 1$) and 2-alkyl-Δ^1-piperideines (**8**, $n = 2$) are readily formed by the methods used to prepare γ- and δ-amino ketones (*3–6*). The reaction of corresponding halogeno ketones with ammonia belongs to the classical reactions of this type.



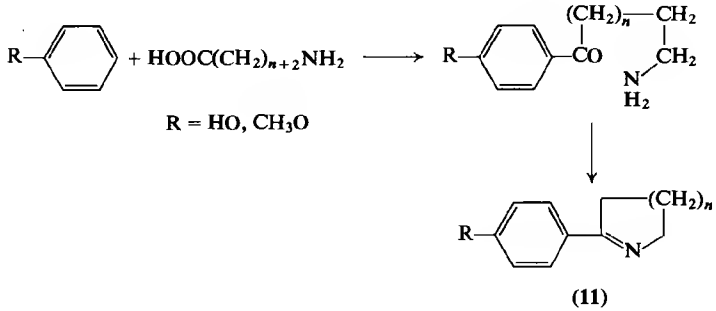
(8)

By use of potassium phthalimide we can isolate the intermediate. α-Oxo-δ-aminovaleric (**9**, $n = 1$) and α-oxo-ε-aminocaproic acids (**9**, $n = 2$) readily yield Δ^1-pyrroline-2-carboxylic acid (**10**, $n = 1$) and Δ^1-piperideine-2-carboxylic acids (**10**, $n = 2$), respectively (*7–10*). The equilibria of the acids with their cyclic forms was observed in water solutions (*11,12*).



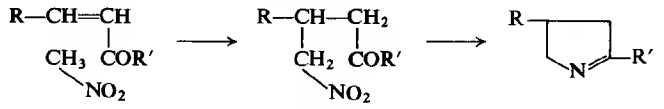
(9) (10)

Phenols and phenol ethers can be acylated with γ- or δ-amino acids in the presence of polyphosphoric acid to form 2-aryl-Δ^1-pyrrolines (**11**, $n = 1$) or 2-aryl-Δ^1-piperideines (**11**, $n = 2$), respectively (*13*).



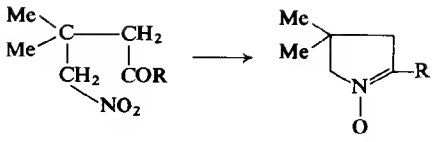
(11)

The use of primary amines instead of ammonia affords 1,2-dialkyl-Δ^2-pyrrolines or 1,2-dialkyl-Δ^2-piperideines. Amino ketones with a primary amino group are intermediates in the reduction of γ-nitropropylalkyl ketones (*14,15*) or δ-nitrobutylalkyl ketones (*16–18*) by catalytic hydrogenation over Raney nickel or with zinc and hydrochloric acid (Scheme 1).



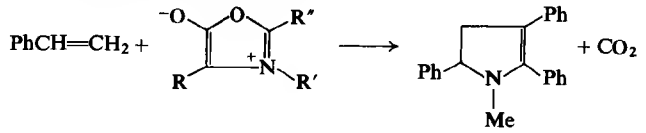
Scheme 1

Δ^1-Pyrroline-N-oxides (**12**) are sometimes isolated when using zinc–ammonium chloride (*19,20*), iron–sulfuric acid (*14*) or hydrazine–Raney nickel (*21*) as reducing agents. During the reduction, dimerization has been often observed (*22*).



(12)

Δ^1-Pyrrolines have been isolated from the hydrogenation products of γ-ketonitriles (*23–26*) and in a large number of reactions during which enamino ketones are formed as intermediates. The preparation of pyrrolines from anhydro-5-hydroxyoxazolinium hydroxides (**13**, R, R″ = Ph, R′ = Me) is also important (*27*). By the reaction of **13** with styrene, 1-methyl-2,3,5-triphenyl-Δ^2-pyrroline (**14**) is formed.

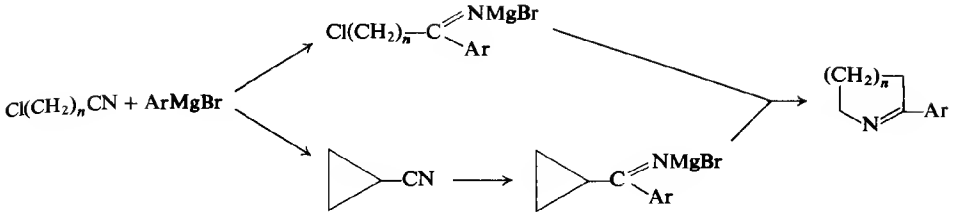


(13) (14)

When the 1-monoximes or dioximes of 4-acetyl-1-tetralones are hydrogenated in the presence of palladium, mixtures of diastereoisomeric 1-aminotetralones are formed. The *cis*-aminoketone isomers readily form dehydrobenzoisoquinuclideines (3,4-disubstituted-1,4-dihydro-1,4-ethanoisoquinolines). Quaternary immonium salts prepared from these bicyclic imines are then converted by bases to bicyclic enamines [2,4-disubstituted-3-alkylidene-1,4-ethano-1,2,3,4-tetrahydroisoquinolines (*28*)].

2. *Preparation of Heterocyclic Enamines by Means of Organometallic Reagents*

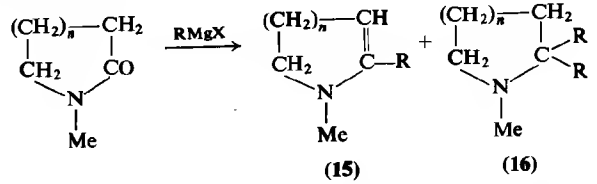
Δ^1-Pyrrolines and Δ^1-piperideines are formed on treatment of γ- and δ-halogenonitriles (*29–34*), respectively, with Grignard reagents. As for the reaction mechanism, it is very probable that the pyrrolines form mainly by a direct thermal displacement of the imine and only to a small extent by rearrangement of the cyclopropylketimine intermediate (*35,36*) (Scheme 2). It has recently been reported that treatment of the cyclopropylnitrile with phenyllithium yields an isolable ketimine (*36a–36c*). Simple thermal rearrangement of the ketimine does not occur at temperatures up to 200° but acid catalyzed thermal rearrangement does occur, producing 2-phenyl-Δ^1-pyrroline in good yield. The quaternary methiodide salt of a ketimine can be thermally rearranged to a Δ^2-pyrroline (*36a–36e*).



Scheme 2

2-Alkyl-Δ^1-piperideines were obtained on treatment of imino ethers with Grignard reagent (*37,38*).

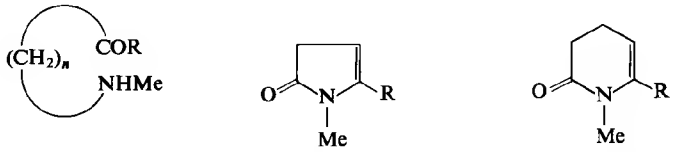
Lukeš studied the reaction of N-methyl lactams with Grignard reagents. With the five- (*39–42*) and six-membered (*43–47*) rings, 2,2-dialkylated bases (**16**, $n = 1, 2$) are formed as by-products in addition to the 1-methyl-2-alkyl pyrrolines (**15**, $n = 1$) or 1-methyl-2-alkyl piperideines (**15**, $n = 2$). Aromatic Grignard reagents afford only the unsaturated bases, probably because of steric factors (*48,49*). Separation of enamines and 2,2-dialkylated amines from each other can be easily achieved since the perchlorates of the enamines and the picrates of 2,2-dialkylated bases crystallize readily. Therefore enamines can be isolated as crystalline perchlorates and the 2,2-dialkylated bases as crystalline picrates. Some authors who repeated the reactions isolated only pyrrolines (*50,51*) or, by contrast, 2,2-dialkylated bases (*52*). This can be explained by use of unsuitable isolation techniques by the authors.



(15) (16)

The reaction was also carried out with variously substituted (*53–55*) and nonmethylated (*56*) lactams. Treatment of 1-methyl-2-piperidone with phenylmagnesium bromide and subsequent reaction with acetic anhydride gave the corresponding acetate in small yield (*57*). This indicates that the carbinolamine salt is an intermediate in this reaction which, on liberation, affords another tautomeric form. In the five- and six-membered series this tautomeric form is a cyclic enamine. Lactams with larger rings, i.e., seven- (*58,59*), eight- (*60*), nine- (*61*), eleven-, and thirteen-membered (*62*) lactams, yield only acyclic amino ketones (**17**, $n = 5$–11) when treated with Grignard

reagents. Treatment of a 1-naphthyl-substituted seven- or thirteen-membered ring with Grignard reagents produces both the enamine and the amino ketone (*63*).

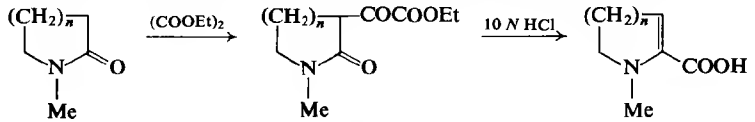


(17) (18) (19)

Treatment of imides of dicarboxylic acids with organometallic compounds forms cyclic enamines such as **18** and **19** (*64–69*).

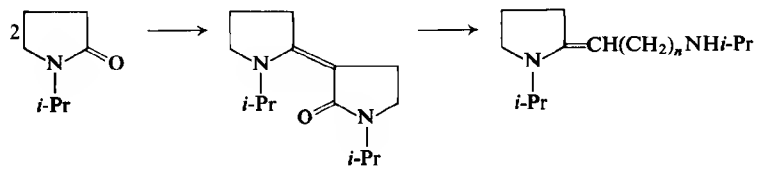
3. *Preparation of Heterocyclic Enamines by Means of Claisen Condensation of Lactams*

The reactivity of the methylene group adjacent to the lactam group affords the possibility of a Claisen condensation. Thus, treatment of 2-pyrrolidone or 2-piperidone with ethyl oxalate leads to the Δ^1-pyrroline-carboxylic (*70*) and Δ^1-piperideine-2-carboxylic acids (*71*), respectively. N-methyl lactams furnish N-methyl derivatives (*72,73*) (Scheme 3).



Scheme 3

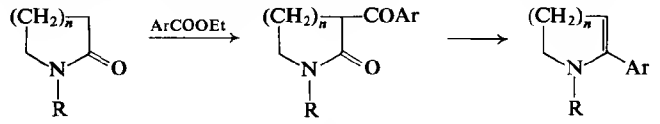
In some cases, the products of Claisen condensation of two molecules of 2-pyrrolidones (**20**) can be hydrolyzed to 2-alkylidenepyrrolidines (**21**) (*74*).



(20) (21)

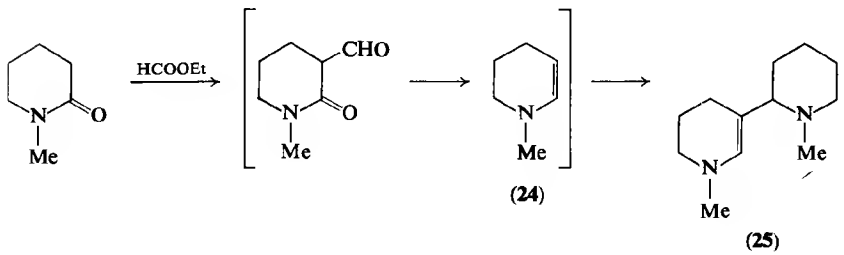
The treatment of esters of aromatic acids with 1-alkyl-2-pyrrolidones and 1-alkyl-2-piperidones is an extremely useful method for the preparation of simple pyrrolines and piperideines, respectively. The 1-alkyl-3-aroyl-2-

pyrrolidones (**22**, $n = 1$) and 1-alkyl-3-aroyl-2-piperidones (**22**, $n = 2$) thus formed are cleaved by the action of concentrated hydrochloric acid to 1-alkyl-2-aryl-Δ^2-pyrrolines (*75*) (**23**, $n = 1$) and 1-alkyl-2-aryl-Δ^2-piperideines (*76*) (**23**, $n = 2$), respectively. After blocking the secondary nitrogen



(22) (23)

atom in a lactam by means of acylation, one can prepare 2-aryl-Δ^1-pyrrolines and 2-aryl-Δ^1-piperideines by the same reaction route (*77*). Treatment of ethyl formate with 1-methyl-2-piperidone yields 1-methyl-2-piperideine (**24**) and, subsequently, dimer (**25**) in alkaline medium (*78,79*).



(24) (25)

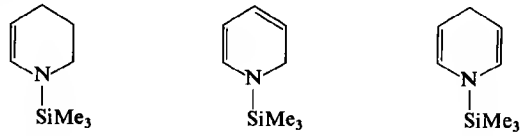
B. Reduction and Elimination Methods

Partial hydrogenation of pyrrole derivatives and partial dehydrogenation of pyrrolidines afford Δ^1-pyrrolines (*80–82*). However, because of the complex nature of the reaction, it is of little preparative value. The same is true for isomerization of Δ^3-pyrrolines to Δ^1-pyrrolines (*83*). A photo-dehydrogenation of 2,6-dimethylpiperidine (**26**) has been observed recently, affording 2,6-dimethyl-3,4,5,6-tetrahydropyridine (**27**) in a good yield (*84*).

(26) (27)

The 1,2-dihydro derivative is formed by reduction of pyridine with $LiAlH_4$ (*85*). Analogous reduction with sodium in 95% alcohol affords the 1,4-dihydro derivative. Monomeric N-trimethylsilyl-1,2,3,4-tetrahydro (**28**)

and the corresponding 1,2-dihydro (**29**) and 1,4-dihydro derivatives (**30**) of pyridine have been prepared by treatment of pyridine with trimethylsilane in the presence of palladium (*86*). Pyridines with a carbonyl function (exemplified by ketones, an ester, and an amide) in the 3 position can be hydrogenated to corresponding 1,4,5,6-tetrahydropyridine derivatives in good yield (*87*).



(28) **(29)** **(30)**

Reduction of quaternary pyridine salts with sodium amalgam or sodium hydrosulfite affords 1,2-dihydro (*88*) and 1,4-dihydro derivatives, respectively. From the preparative point of view, partial hydrogenation of quaternary pyridine salts in alkaline media to give substituted 1-methyl-Δ^2-piperideines is very important (*89,90*). Formation of 1,2-dihydroisoquinolines was observed in the reduction of quaternary isoquinoline salts with sodium hydrosulfite (*91*), lithium aluminum hydride (*92,93*), dialkylaluminohydrides (*94*) or on treatment with Grignard reagent (*95*). 1,2- and 1,4-dihydro derivatives were also formed from 3,5-dicyanopyridines by reduction with sodium borohydride (*96*) or by reaction with Grignard reagent (*97*). Formation of enamines was observed in the reduction of 1-methyl-2-piperidone with sodium in ethanol (*98*) or lithium aluminum hydride (*99*). Electroreduction of N-methylglutarimide likewise produces enamines (*100,101*).

Δ^1-Pyrroline has been prepared in low yield by oxidation of proline with sodium hypochlorite (*71*), persulfate (*102*), and periodate (*103*). Δ^1-Pyrroline and Δ^1-piperideine are products of enzymic oxidation via deamination of putrescine and cadaverine or ornithine and lysine, respectively (*104,105*). This process plays an important part in metabolism and in the biosynthesis of various heterocyclic compounds, especially of alkaloids.

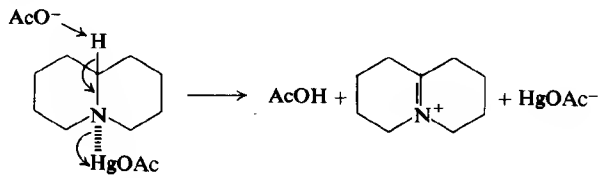
The best procedure for the preparation of Δ^1-pyrroline (**31**, $n = 1$) and Δ^1-piperideine (**31**, $n = 2$) consists of dehydrohalogenation of N-chloropyrrolidine and N-chloropiperidine, respectively, by means of potassium hydroxide (*106*).

(31)

Δ^1-Piperideine-N-oxide was obtained along with a dimeric product by oxidation of N-hydroxypiperidines with mercuric acetate or potassium ferricyanide (*107–109*). Δ^1-Pyrroline-N-oxide is formed by oxidation of N-ethylpyrrolidine with hydrogen peroxide with simultaneous formation of ethylene (*110*).

Another convenient method for the preparation of tertiary enamines involves the dehydrogenation of saturated bases with mercuric acetate (*111–116*). A *trans*-1,2 elimination occurs, which requires an antiperiplanar position of the nitrogen-free electron pair and the eliminated atom. A preferential elimination of the hydrogen atom from the tertiary carbon atom is supposed. Overoxidation can be avoided by adding disodium ethylenediaminotetraacetate to the reaction mixture (*117*).

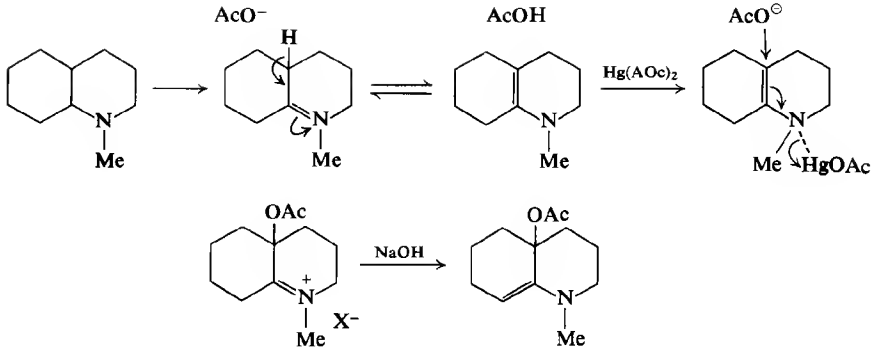
Bohlmann et al. (*118–121*) observed that an infrared absorption band between 2700–2800 cm^{-1} is characteristic of a piperidine derivative possessing at least two axial carbon–hydrogen bonds in antiperiplanar position to the free-electron pair on the nitrogen atom. The possibility of forming an enamine by dehydrogenation can be determined by this test. Compounds which do not fulfill this condition cannot usually be dehydrogenated (*50, 122,123*). Thus, for example, yohimbine can be dehydrogenated by mercuric acetate,whereas reserpine or pseudoyohimbine do not react (*124*). The quinolizidine (*125*) enamines (Scheme 4), 1-azabicyclo(4,3,0)-nonane, 1-azabicyclo(5,3,0)decane, 1-azabicyclo(5,4,0)undecane, and 1-azabicyclo(5,5,0)dodecane have been prepared in this manner (*112,126*).



$$HgOAc^- + Hg(OAc)_2 \longrightarrow Hg_2(OAc)_2 + OAc^-$$

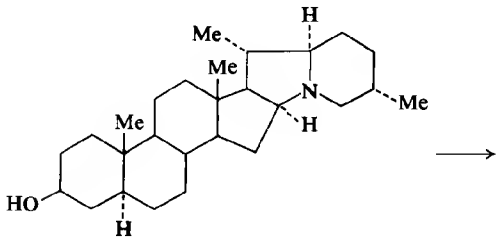
Scheme 4

The dehydrogenation of 4-aryl quinolizidines is very interesting, too. The double bond of the salts is formed in the $\Delta^{9,10}$ position and not in the expected $\Delta^{4,10}$ position (*127*). In several cases, hydroxylation takes place in the dehydrogenation of 1-methylquinolizidine (*115*), especially of *cis*- and *trans*-1-methyldecahydroquinolines (*128,129*) (Scheme 5).



Scheme 5

5α,22αH,25βH-Solanidanole-3 (**32**) is one of several complex compounds containing an indolizidine skeleton which can be dehydrogenated by mercuric acetate as well as by N-bromosuccinimide, yielding in this case a mixture of immonium salts, namely, $\Delta^{22(N)}$-5α,25βH-solanidenole-3β (**33**), and $\Delta^{16(N)}$-5α,22αH,25βH-solanidenole-3β (**34**) (*130*).



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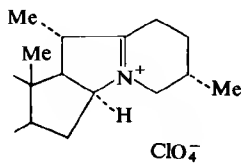

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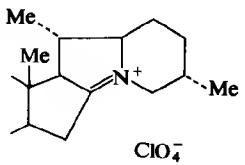
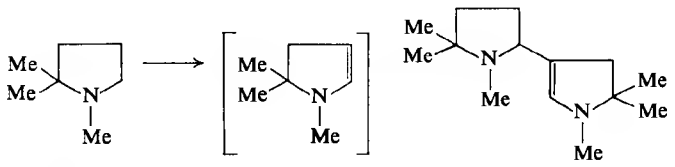


(34)

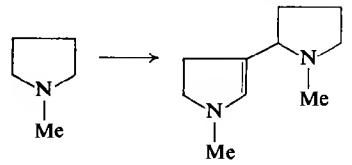
The 1,2-, 1,2,5-, 1,3,4-, and 1,2,5-substituted pyrrolidines afford the corresponding pyrrolines very readily by oxidation with mercuric acetate. In the case of 1,2,2-trimethylpyrrolidine (**35**), the formation of a double bond

involving the unsubstituted α-carbon atom is followed by dimerization of the intermediate (**36**) to 1,5,5-trimethyl-3-(1′,5′,5′-trimethyl-2′-pyrrolidyl)-Δ^2-pyrroline (**37**) (*131*). The formation of oligomers is a frequent complication in the preparation of enamines. Dehydrogenation of 1-methylpyrrolidine (**38**) gives dimer (**39**) in addition to a trimer which is identical with a



(35) (36) (37)

product obtained by the reduction of N-methylpyrrole with zinc and hydrochloric acid (*131,132*). A dimer is formed by analogous dehydrogenation of

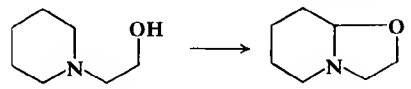


(38) (39)

1,3-dimethylpyrrolidine. In the same manner 1,3,4-trimethylpyrrolidine is dimerized and oxidized to 2-(1′,3′,4′-trimethyl-2′-pyrrolidyl)pyrrole (*131*).

Dehydrogenation of 1-methyl-1-azacycloheptane through azacyclononane, followed by treatment with hydrogen sulfide, gave the trithiane derivatives only (*132a*). These results give further evidence about the instability of enamines with medium-sized rings.

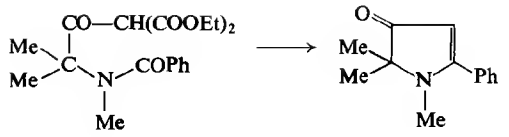
Dehydrogenation of amino alcohols of type **40** affords even bicyclic compounds **41**, the formation of which can be explained by nucleophilic attack of the hydroxyl group on the formed enamine salt (*133,134*).



(40) (41)

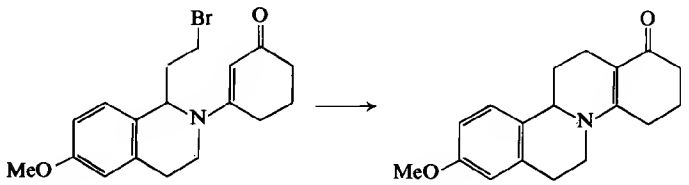
C. Preparation of Enamino Ketones

Acylated alkyl aminoisobutyrylmalonates (**42**) can be easily converted to 3-oxo-Δ^2-pyrrolines (*135,136*) (**43**).



(42) (43)

The general method for preparation of heterocyclic enamino ketones, amide vinylogs, consists of a cyclization reaction (Scheme 6). The most convenient technique involves heating the starting substance in acetonitrile in the presence of silver perchlorate (*137–139*).



Scheme 6

The preparation of enamine ketones by addition of α,β-unsaturated ketones to enamines is described in Chapter 4.

III. Structure and Physicochemical Properties

The presence of an enamine grouping in a molecule makes possible several interconvertible structures. The application of physicochemical methods has been of greatest importance for determining the actual structure. Unsaturated amines with the double bond separated from the nitrogen atom by one saturated carbon atom do not show behavior different from other organic bases, and the character of the double bond corresponds to that of other unsaturated compounds. The shift of a double bond to the α,β position in respect to nitrogen atom leads, by contrast, to the formation of a new reactive grouping in which the nitrogen-free electron pair is conjugated with the π electrons of the double bond. The mesomeric character of an enamine grouping is then exemplified by the fact that reaction may occur on either the nitrogen or β-carbon atom of the grouping, an increased basicity of the molecule, and change in the spectral properties of the double bond.

A. Pyrrolines and Piperideines

1. *Secondary*

As pointed out in the introduction, if one of the substituents on the nitrogen atom is a hydrogen atom, tautomeric equilibrium between enamino and imino forms strongly favors the latter form (*18,140,141*). According to physiochemical measurements, the occurrence of simply substituted Δ^2-pyrrolines and Δ^2-piperideines is very improbable. The formulation of this type of compound with a double bond in the Δ^2 position (used mainly by early authors) was of formal meaning only, having no experimental evidence (*142–144*).

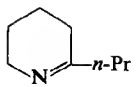
A study of infrared and NMR spectra makes it possible to distinguish between both tautomeric structures (*145–147*). A single strong absorption band at 1620 cm^{-1}, attributable to the carbon–nitrogen double bond, has been found in the infrared spectra of 2-alkyl pyrrolines (**44**, R = alkyl) and 2-aryl pyrrolines (*148*) (**44**, R = aryl); but absorption at 3300 cm^{-1} due to the presence of the N—H group was not present. The estimation of an active hydrogen, which is in every reported case negative, leads to the same conclusions (*144,149*). The determination was even negative with 2,3-diphenyl-Δ^1-pyrroline (**45**), where the probability of the Δ^2-structure stabilization ought to be higher (*150*). It is, nevertheless, expected that

(44) (45)

conjugation would support the enamine structure. According to spectral data, 2-benzylpyrroline exists as a mixture of both imino and enamino tautomers, the enamino form possessing an exocyclic double bond, whereas the negative estimation of active hydrogen points to its existence solely in Δ^1 form (*144*).

The piperideine derivatives have not been studied as extensively as the analogous pyrrolines (*151,152*). The imino structure has been established, for example, for the alkaloid γ-coniceine (*146*) (**46**). The great influence of conjugation on the structure is seen with 1-(α-picolyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (**47**), possessing an enamine structure, whereas the analogous 1-methyl derivative (**48**) possesses an imine structure according to infrared spectra (*152,153*).

In contrast to the five-membered ring, conformational factors would be expected to influence the equilibrium between the imine and enamine forms in the case of the six-membered-ring piperideine derivatives (*154*).



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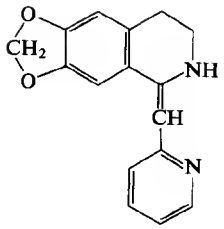

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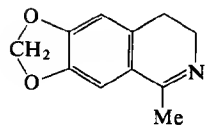
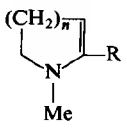


(48)

2. *Tertiary*

Tertiary pyrrolines (**49**, $n = 1$) and piperideines (**49**, $n = 2$) (if R = H and the enamine can exist in the monomeric form or if R = aryl) evidently possess an endocyclic Δ^2-double bond (*79,155,156*). The stretching frequency of the double bond can be lowered to 1620–1635 cm^{-1} by conjugation with an aromatic substituent. The double bond of an analogous compound with aliphatic substituents in position 2 may occupy either the endo or the exo position. Lukeš and co-workers (*157*) have shown that the majority of the five-membered-ring compounds, traditionally formulated with the double bond in a Δ^2 position, possess the structure of 2-alkylidene derivatives (**50**) with an exocyclic double bond, infrared absorption at 1627 cm^{-1}. Only the 1,2-dimethyl derivative (**51**) is actually a Δ^2-pyrroline, absorbing at 1632 cm^{-1}. For comparison, 1,3,3-trimethyl-2-methylene pyrrolidine (**52**) with an unambiguous exocyclic double bond has been prepared (*54*).



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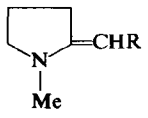

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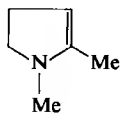

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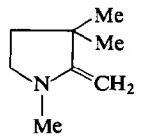
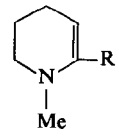


(52)

The ultraviolet spectra were also used for determination of the pyrroline structure (*1,158–160*). They exhibit a bathochromic shift to 225–235 mμ, caused by the auxochromic action of the nitrogen-free electron pair which is in conjugation with π electrons of the enamine double bond (*161,162*).

More complex compounds containing enamine grouping, e.g., holarrhena alkaloids such as conkurchine and conessidine, possess an endocyclic rather than exocyclic double bond (*159*). On the other hand, 1-methyl-2-alkylpiperideines (**53**) possess a fixed endocyclic double bond (*163,164*) ($\nu_{C=C}$ 1635–1645 cm^{-1}), probably because of higher endocyclic double bond stability in six-membered rings (*165,166*).



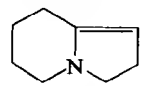
(53)

B. ENAMINES OF 1-AZABICYCLOALKANES

Enamines derived from 1-azabicycloalkanes, readily accessible by mercuric acetate oxidation of saturated bases (*112*), have been extensively studied recently (*113–115*). Since an immonium salt is formed during dehydrogenation, the composition of the liberated enamine mixture shows the relative stability of the various possible isomers. The study of infrared and NMR spectra has shown that the position of the enamine double bond is determined by factors similar to those determining the relative stability of simple olefins.

a. In the case of enamines which can exist in two different isomeric forms (for example, indolizidine derivatives) the equilibrium is strongly in favor of that isomer containing the double bond in the endo position to a six-membered ring and in the exo position to a five-membered ring.

The enamine formed by dehydrogenation of indolizidine was considered to be a mixture of $\Delta^{1,9}$ (**54**) and Δ^8 (**55**) isomers because of infrared spectra (*126*). According to the NMR spectrum, the Δ^8 isomer is the major constituent. This is demonstrated by comparison of this spectrum with the spectra of compounds **56** and **57** containing fixed double bonds.



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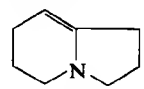

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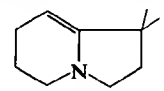

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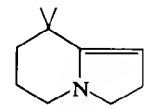
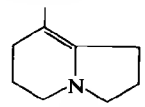


(57)

The 8-methyl derivative (**58**) and 1-ethyl derivative (**59**) were shown to possess mainly the Δ^8 structure, while the 1-methyl derivative contains the Δ^8, structure in the ratio 2:1.



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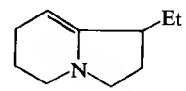
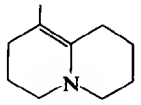
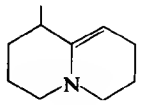


(59)

b. Substituents stabilize the double bond. The enamine of 1-methylquinolizidine exists as a mixture of $\Delta^{1,10}$ isomer (**60**) and Δ^{9} isomer (**61**) in a 2:1 ratio.

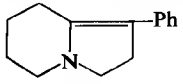


(**60**)

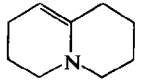


(**61**)

c. Formation of enamine stabilized by conjugation is preferred. Dehydrogenation of 1-phenylindolizidine affords the $\Delta^{1,9}$-1-phenyl isomer (**62**) only.



(**62**)



(**63**)

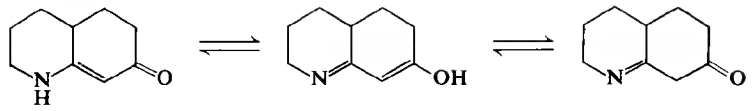
The infrared spectrum of $\Delta^{1,10}$-dehydroquinolizidine (**63**) exhibits an absorption maximum at 1652 cm^{-1}, and the ultraviolet spectrum shows a maximum at λ_{max} 228 mμ (ϵ_{max} 5600). Nuclear magnetic resonance spectra of all compounds in question possess four proton-absorption regions. Vinyl protons H—C=C exhibit broad singlets and sometimes a poorly resolved triplet centered at τ 5.65–5.98 ppm. Unusually high chemical shifts can be explained by considering mesomeric contributors. Protons of methylene groups attached to a nitrogen atom —CH_2—N— lead to broad triplets or multiplets centred at τ 7.1–7.3 ppm. Methyl group protons CH_3—C= exhibit peaks at τ 8.4–8.5 and 8.8–9.0 ppm, typical for an allylic grouping. The other protons produce very broad multiplets at τ 7.5–8.5 ppm.

C. Enamino Ketones

Structural analogy of aliphatic amino ketones can be found in the heterocyclic series. A simple example of such compounds is $\Delta^{8,9}$-octahydro-7-quinolone (*167*) which, as a vinylog of an amide, can possess enonamine–enolimine tautomerism (*168*).

The infrared, ultraviolet and NMR spectra of $\Delta^{8,9}$-octahydro-7-quinoline were compared with the corresponding spectra of the N-ethyl and O-ethyl derivatives in order to determine whether it is in the enamine (**64**), enolimine (**65**), or ketimine (**66**) form.

The infrared spectrum exhibits absorption maxima at 3405 cm^{-1} (NH), 1610 cm^{-1} (C=O), 1580 cm^{-1} (C=C) without any band at 3610 cm^{-1}



(**64**) (**65**) (**66**)

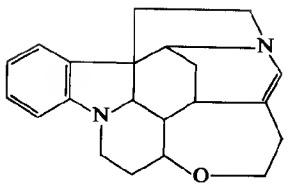
due to enolic hydroxyl group. Spectra of corresponding N-ethyl derivatives contain absorption maxima at 1600 cm^{-1} (C=O) and 1550 cm^{-1} (C=C) while those of O-ethyl derivatives show a broad band at 1628 cm^{-1} due to the presence of C=N and C=C double bonds. In the ultraviolet spectrum of the unsubstituted compound an absorption maximum at λ_{max} 298 mμ (log ϵ 4.49) was observed, while the N-ethyl derivative showed a maximum at λ_{max} 304 mμ (log ϵ 4.97) and the O-ethyl derivative showed quite a different maximum at λ_{max} 245 mμ (log ϵ 4.21). The NMR spectrum consists of a singlet due to vinyl protons with chemical shift δ 5.18 ppm (the same singlet is exhibited by the N-ethyl derivative at δ 5.21 ppm and the O-ethyl derivative at δ 5.33 ppm) and a broad singlet at δ 5.9 ppm due to the NH-group proton. These data indicate unambiguously enamine structure **64**. The study of spectra of $\Delta^{9,10}$-octahydro-5-quinolone leads to a similar conclusion.

D. Enamines that Cannot Exhibit Mesomerism

Mesomerism involving polarized and nonpolarized contributing enamine forms influences the enamine's spectral properties and chemical reactivity. For mesomerism to be present, a planar arrangement is required for the three atoms of enamine grouping and the five atoms immediately bound to this system. If this condition is not fulfilled, full interaction of the π electrons of the double bond with the free electron pair on the nitrogen atom is impossible. Enamines in which mesomerism is inhibited do not show the properties characteristic of enamines, and only the mutual electrostatic interaction of the double bond and lone electron pair of the nitrogen atom can be observed. Such steric hindrance of mesomerism occurs mainly in polycyclic systems.

The simplest examples of this type of compound are enamines derived from the quinuclidine skeleton (**67**). The formulation of enamines of quinuclidine in a mesomeric form would violate Bredt's rule. Actually, the ultraviolet spectrum of 2,3-benzoquinuclidine shows that there exists no interaction of aromatic ring π electrons and the nitrogen-free electron pair (*160,169*). The overlap of the olefinic π orbital and the lone pair orbital on nitrogen is precluded.

(67)



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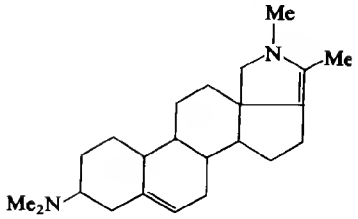


(69)

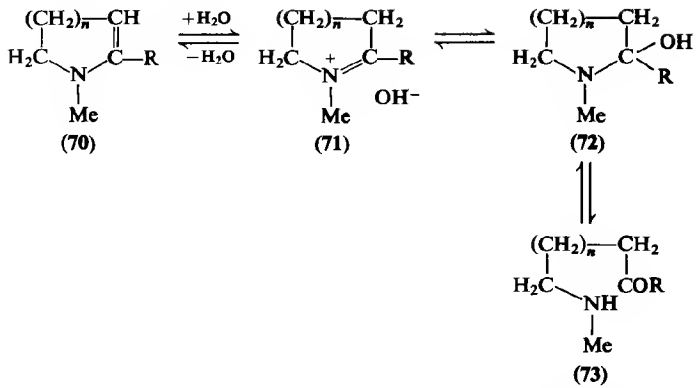
Similar behavior can be observed even in the case of substituted quinuclideines (*170*). Neostrychnine (**68**) serves as an example of more complex compounds which show spectra differing from those of other enamines. The ultraviolet spectrum of this compound exhibits no bathochromic shift and its basicity is considerably decreased (*159,171,172*) (pK_a in methylcellosolve at 20° is 3.8, whereas the analogous saturated compound has a pK_a under the same conditions of 7.45, and a compound with the double bond further removed, strychnine, has a pK_a of 7.37). As another example, the ultraviolet spectrum of trimethyl conkurchine (**69**) shows the same absorption maxima as a saturated tertiary amine (λ_{max} in ether, about 213 mμ).

E. Tautomerism of Enamines

The study of structure and reactivity of tertiary heterocyclic enamines is associated with the problem of equilibrium of the cyclic enamine form (**70**) and the tautomeric hydration products (*173,174*): quaternary hydroxide (**71**), pseudo base (so-called carbinolamine) (**72**) and an opened form of amino aldehyde or amino ketone (**73**).

The position of the equilibrium is determined not only by ring size and polar and steric factors but also by the environment of the molecule. The experimental evidence for the existence of three tautomeric forms has been based on the study of their reactivity and, to a lesser degree, on physicochemical measurements (*175–177*). Often the existence of the corresponding carbinolamine or its acyclic tautomeric form in addition to the basic dehydrated form is quite important.

Five- (**70**, $n = 1$) and six-membered (**70**, $n = 2$) enamines substituted in position 2 generally exist in the cyclic form. Lukeš and co-workers observed that partial ring-opening occurs with the pyrroline (*157*) or piperideine (*163,164*) derivatives by atmospheric moisture. This leads to the formation



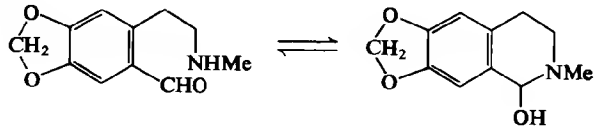
(70) (71) (72) (73)

of amino ketones, which can be detected by the ketonic carbonyl absorption at 1705–1710 cm^{-1} in the infrared spectra. Higher basicity in water solution indicates the presence of quaternary hydroxide **71** (pK_a of 1,2-dimethyl-Δ^2-pyrroline is, for example, 11.94, and that of the corresponding saturated compound is 10.23. The analogous six-membered compound has pK_a 11.43, and the corresponding saturated base, 10.26 (*1,51*). Introduction of a double bond in the α,β position of primary and secondary amines causes, by contrast, a decrease of basicity (*31,178*). The five- and six-membered enamines unsubstituted in position 2 generally exist in cyclic form also.

On the other hand, the cyclic form of the analogous seven- to thirteen-membered compounds is energetically disadvantageous and easy formation of amino ketones is encountered. In accordance with this, the compound unsubstituted in position 2 (1-methyl-1-aza-2-cyclooctene, -nonene, and -decene) can react as acyclic amino aldehydes (*176*). In the case of enamines bearing an aromatic ring in position 2, especially with seven- and thirteen-membered rings, a higher stability of the cyclic form can be expected. Therefore there is a good possibility for the isolation of the cyclic form.

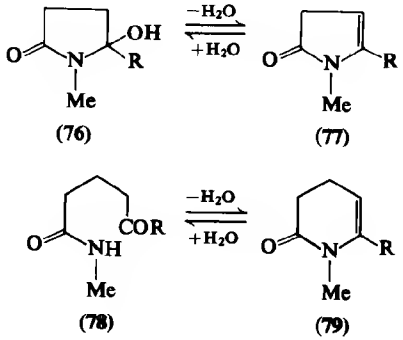
On treatment of 1-naphthylmagnesiumbromide with corresponding N-methyllactams, cyclic enamines 1-methyl-2-α-naphthyl-1-aza-cycloheptene (**70**, $n = 3$) and 1-methyl-2-α-naphthyl-1-aza-cyclotridecene (**70**, $n = 9$) have been prepared. Infrared spectra of the enamines exhibit absorption maxima in the region of C=C double bond vibrational frequencies at 1625–1630 cm^{-1}. These maxima correspond to double bonds in conjugation with an aromatic ring. Salts of these enamines undergo ring opening in alkaline media to produce open amino ketones 6-methylamino-1-α-naphthyl-1-hexanone (**73**, $n = 3$) and 12-methylamino-1-α-naphthyl-1-dodecanone (**73**, $n = 9$).

Compound **74** belongs to a special group which forms cyclic aldehyde ammonia **75** (cotarnine) by interaction of the secondary amine group with the aldehyde group. This aldehyde ammonia can be considered to be a pseudo base.



(74) (75)

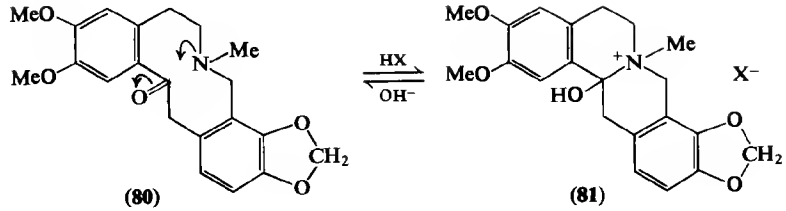
The importance of ring size holds also for tautomerism of Δ^2-pyrrol-5-ones and Δ^2-dihydro-6-pyridones. While the former compounds behave as cyclic 1-methyl-2-alkyl-2-hydroxy-5-pyrrolidones (*179*) (**76**) [or, on distillation, as the dehydrated 1-methyl-2-alkyl-Δ^2-pyrrolones (**77**)], the latter compounds exist as acyclic N-methylamides of δ-oxo-acids (**78**) [as shown by infrared spectroscopy (*180*)]. The dehydration of **78** during distillation to form 1-methyl-2-alkyl-Δ^2-dihydro-6-pyridones (**79**) is achieved only with difficulty.



(76) (77)

(78) (79)

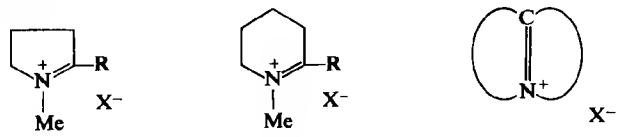
In this area of keto amino reactions, transannular cyclization reactions between the ketonic carbonyl group and the tertiary amino nitrogen atom in medium-sized rings are of great interest (*175,181–183*). In addition to the alkaloid cryptopine (**80**), which is the most usual example, there exists a large number of other simple examples. The main driving force for the cyclization of **80** upon acidification to compound *81* is the tendency to relieve the nonbonding interactions present in the medium-sized ring and to form a conformationally more favorable arrangement. This transannular reaction corresponds to the tautomeric equilibrium between carbinolamine and amino ketone.



(80) (81)

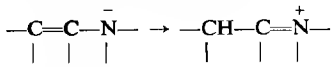
F. Structure of Enamine Salts

Physicochemical investigations of enamines and their salts have shown that the addition of a proton occurs almost exclusively at the β-carbon atom of the enamine grouping. This means that salts of pyrrolines (**82**), piperideines (**83**), and enamines of 1-azabicycloalkanes (**84**) possess immonium structures.



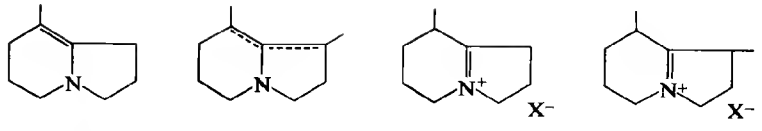
(82) (83) (84)

Structural differences between the free enamine and its salt are accompanied by several spectral changes. The presence of these spectral changes can serve as evidence of the presence of an enamine grouping in the molecule. Usually the presence of the new immonium chromophore is indicated by a marked shift of the absorption maximum in the double-bond stretching region to a higher frequency (20–50 cm^{-1}) from that present in the free enamine (*153,184,185*). This shift, which is very characteristic of enamines, in contrast to β,γ-unsaturated tertiary amines (*171*), was for a long time considered to be an unambiguous criterion of the presence of enamine grouping in the molecule (*115*). However, it has been shown recently in a few cases that structural change



found, for example, when enamines **85** and **86** are treated with acid to form salts **87** and **88**, respectively (immonium structure of which follows from interpretation of NMR spectra), is not accompanied by any increase of characteristic frequency (*155*).

This shift in the infrared spectrum is practically independent of the anion properties.



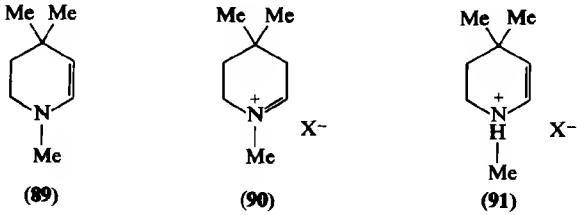
(85) (86) (87) (88)

The study of NMR spectra (*186*) shows that all the Δ^1-pyrrolinium and the Δ^1-piperideinium salts exist as such. The NMR spectra of the pyrrolinium derivatives are especially clearly resolved. The chemical shift for the ring protons in the 5, 3, and 4 position lies to increasing field in this order, as is to be expected. The signals of the methylene groups in the 3 and 5 position are triplets, evidently splitting from the 4 position. The piperideine spectra are less regular; although multiplets for the 3- and 6-methylene groups can be distinguished, the 4- and 5-proton signals are merged. Also the signals for the 3- and 6-methylene groups are in the form of broad peaks representing unresolved multiplets. This difference is evidently connected with the different geometry of the five- and six-membered rings.

The immonium salts derived from 1-azabicycloalkanes have very characteristic NMR spectra (*115,116*), as illustrated by the spectrum of $\Delta^{4,9}$-indolizinium perchlorate. Assignments of the peaks at $\tau = 5.85$ and 6.30 ppm to the $-CH_2-\overset{+}{N}=$ groups and those at $\tau = 6.80$ and 7.21 ppm to the $-CH_2-C=$ groups were based on their relative areas (two protons each) and on the previous observation that the chemical shift of the former type of proton is at lower field than that of the latter.

The ultraviolet absorption at λ_{max} 222–232 nm is comparable only with immonium structure (*186a*). No active hydrogen (Zerewitinov) was present in the immonium salts (*1,186b*) and no deformation vibrations of nitrogen–hydrogen linkage were detected (*186a*).

Cases where the proton is localized on the nitrogen atom and an ammonium salt is formed are exceptional. Salts of 1,4,4-trimethyl-Δ^2-piperidine (**89**), which consist of a mixture of immonium (**90**) and ammonium (**91**) salts, serve as an example (*1*).



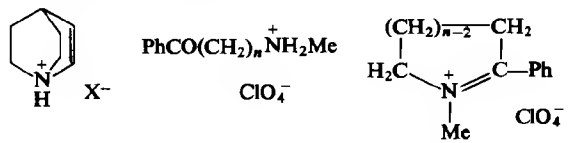
(89) (90) (91)

With imines, salts formation is accompanied by characteristic spectral changes (*153*): (a) a bathochromic shift in the ultraviolet region by as much as 50 mμ, according to compound type and to properties of any auxochrome present, and (b) a high frequency shift of the

stretching vibration in the infrared region. The imine salts possess an active hydrogen, whereas their quaternization products exhibit the same spectral properties as the enamine salts (*187*).

Enamines in which the double-bond shift is sterically prevented afford only the ammonium salts. Their spectra in the C=C stretching vibration region does not differ greatly from that of the free amine spectrum (*171*). For example, neostrychnine (*159*) has $\nu_{C=C}$ at 1666 cm^{-1} and its perchlorate at 1665 cm^{-1}. Salts of quinuclideine (**92**) and the polycyclic alkaloid trimethylconkurchine have similar properties.

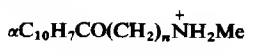
The salts of some enamines crystallize as hydrates. In such cases it is possible that they are derived from either the tautomeric carbinolamine or the amino ketone forms. Amino ketone salts (**93**) ($n = 5$, 11) can serve as examples. The proton resonance spectra of **93** show that these salts exist in the open-chain forms in trifluoroacetic acid solution, rather than in the ring-closed forms (**94**, $n = 5$, 11). The spectrum of the 6-methylamino-1-phenylhexanone cation shows a multiplet at about 2.15 ppm for phenyl, a triplet for the N-methyl centered at 7.0 ppm and overlapped by signals for the methylene protons at about 8.2 ppm. The spectrum of **93** ($n = 11$) was similar. These assignments were confirmed by determination of the spectrum in deuterium oxide. Here the N-methyl group of **93** showed a sharp singlet at about 7.4 ppm since the splitting in $-ND_2Me^+$ was much reduced from that of the undeuterated compound.



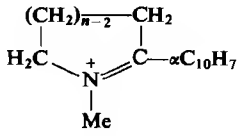
(92) (93) (94)

On the other hand there have been isolated salts of either the acyclic amino ketone form or the cyclic enamine form, namely: 6-methylamino-1-α-naphthyl-1-hexanone (**95**, $n = 5$) and 12-methylamino-1-α-naphthyl-1-dodecanone (**95**, $n = 11$), or 1-methyl-2-α-naphthyl-1-aza-2-cycloheptene

(**96**, $n = 5$) and 1-methyl-2-α-naphthyl-1-aza-2-cyclotridecene (**96**, $n = 11$), respectively (*63*).

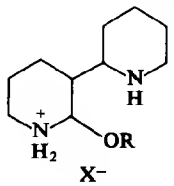


(**95**)

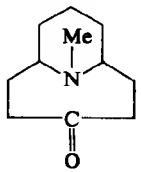


(**96**)

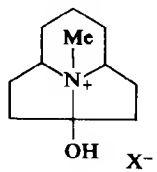
Schöpf et al. (*188,189*) observed that Δ^1-tetrahydroanabasine salts contain a molecule of water or methanol. According to infrared spectra, they exist as 2-hydroxy- or 2-methoxy-3-(2-piperidyl)piperidine salts (**97**). Salt **99**, obtained by a transannular cyclization reaction taking place on neutralization of bicyclic amino ketone **98**, also belongs to this group (*181*).



(**97**)

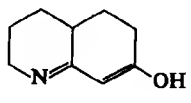


(**98**)

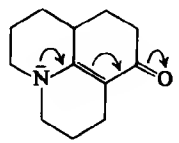


(**99**)

If other groups capable of conjugation are adjacent to the enamine grouping they can also participate in the salt formation. Thus for example, β-amino-α,β-unsaturated ketones can undergo protonation on the carbonyl oxygen atom as well as possible protonation at the carbon and nitrogen atoms. Salts of $\Delta^{8,9}$-octahydro-7-quinolone (**64**) have their proton situated on the oxygen atom (**100**) (*168*). The evidence for this structural assignment comes mainly from the hypsochromic shift in the ultraviolet absorption spectrum [the free base exhibits λ_{max} 298 mμ (log ε 4.53) and the salt λ_{max} 280 mμ (log ε 4.30)]. Salts of tertiary enamino ketone **101** are formed in a similar manner.



(**100**)



(**101**)

IV. Reactions of Heterocyclic Enamines

The double bonds of either enamines or their salts readily undergo many reactions. We shall divide the reactions of heterocyclic enamines on the basis of the mechanism involved.

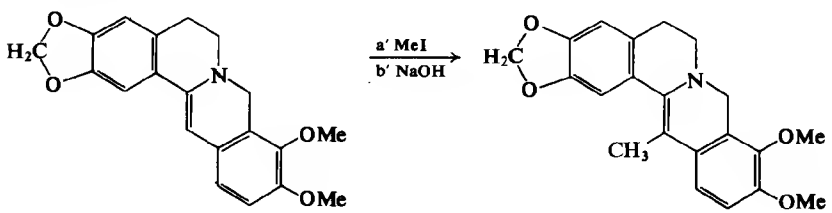
A. Reactions of Electrophilic Reagents with the Double Bond of Enamines

Since there are two available sites for electrophilic attack in an enamine, the electrophile can add to the nitrogen atom to form an ammonium salt, or it can add to the β position to form an immonium salt.

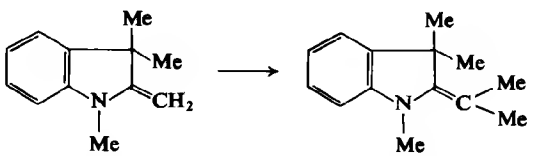
1. *Alkylation and Acylation*

All enamines do not react in the same way. Both reactive sites are available for electrophilic alkylation. Whether the alkylation occurs on the nitrogen or the carbon atom depends on the reactivity of the alkylation reagent, the structure of the enamine, and finally the polarity of the solvent. Aliphatic alkylating reagents exhibit a greater tendency to react with the nitrogen atom to form quaternary ammonium salts. The more reactive alkyl halides such as allyl halides, α-halogeno ketones, and α-halogeno esters would, by contrast, react mainly with the β-carbon atom of the enamine grouping.

The first reported alkylations at the β-carbon atom of a heterocyclic enamine were observed with the alkylations of dihydroberberine (**102**) (*190,191*) and 1,3,3-trimethyl-2-2-methyleneindoline (*192,193*) (**104**) to yield monomethylated products **103** and 1,3,-trimethyl-2-isopropylidene-indoline (**105**), respectively.

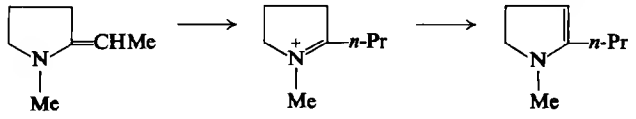


(**102**) (**103**)



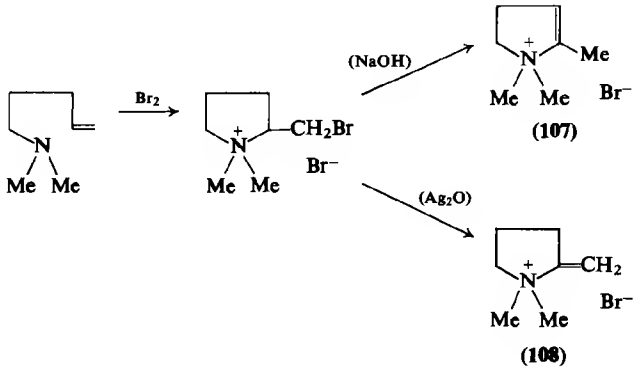
(**104**) (**105**)

C alkylation was used in the corydaline synthesis (*194*). Lukeš and Dědek (*195*) obtained on methylation of 1-methyl-2-ethylidenepyrrolidine a C-alkylation product, i.e., 1-methyl-2-isopropyl-Δ^2-pyrroline (**106**). Alkylation of the same enamine with ethyl bromoacetate was the first synthetic step in the preparation of D,L-pseudoheliotridane (*196*).



(106)

Quaternary ammonium salts of pyrrolines (*106*) can be prepared only indirectly (*197*). Addition of bromine to 1-dimethylamino-4-pentene followed by removal of hydrogen bromide afforded, depending upon the dehydrohalogenation conditions, quaternary bromides derived from either 1,2-dimethyl-Δ^2-pyrroline (**107**) or 1-methyl-2-methylenepyrrolidine (**108**) (Scheme 7).

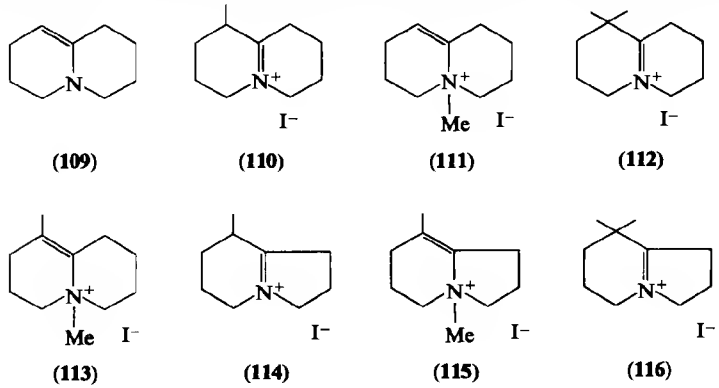


Scheme 7

Hofmann degradation of 1,1-dimethyl-2-methylenepyrrolidinium hydroxide furnishes dimethylamine and dimethyl-3-pentynylamine (*198*). 1,1,4,4-Tetramethyltetrahydropyridinium hydroxide was obtained from 1-dimethylamino-4,5-dibromopentane by means of silver oxide. Hofmann degradation of the product gives 1,4,4-trimethyl-Δ^2-tetrahydropyridine (*199*).

A study of methylation of 1-azabicycloalkane enamines shows the complexity of the alkylation reaction. Treatment of $\Delta^{1,10}$-dehydroquinolizidine (**109**) with methyliodide (*111,113*) gives a mixture of three products

(**110**, **111**, and **112**) containing 83% of the quaternary ammonium salt **111**. 1-Methyl-$\Delta^{1,10}$-dehydroquinolizidine (**60**) affords ammonium salt **113** only.



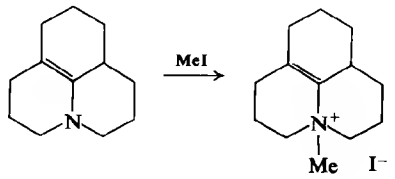
Upon methylation of Δ^8-dehydroindolizidine (**55**), dialkylated compounds **115** and **116** are formed in addition to C-monomethylated product **114**. Compound **115** is accessible also by methylation of 8-methyl-Δ^8-dehydroquinolizidine (*113*).

It is noteworthy that only in the case of dehydroquinolizidine derivatives does monomethylation produce the N-alkylated product. The formation of dialkylated products can be explained by a disproportionation reaction of the monoalkylated immonium salt caused by either the basicity of the starting enamine or some base added to the reaction mixture (most often potassium carbonate) and subsequent alkylation of the monoalkylated enamine. Reinecke and Kray (*113*) try to explain the different behavior of $\Delta^{1,10}$-dehydroquinolizidine and Δ^8-dehydroquinolizidine derivatives by the difference in energies of N- and C-alkylation transition states because of the presence of I strain.

In the case of methylation of Δ^8-dehydroindolizidine on nitrogen, the orbitals of nitrogen in such a planar system would have to rehybridize from trigonal to tetragonal configuration, which is not advantageous for nitrogen as a part of a five-membered ring, because of I strain. The analogous β-carbon atom (of the enamine system) hybridization is more favorable in the transition state since this atom is solely a part of a six-membered ring (*200*). With quinolizidine enamines, where the nitrogen atom is a part of two six-membered rings, the sp^3 rehybridization in the transition state of N methylation does not require a substantial increase of activation energy for the reaction. It is important to point out that more reactive halides such

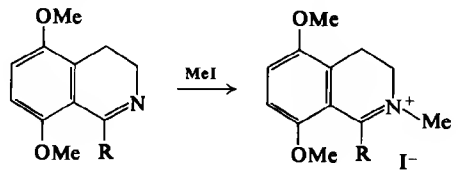
as allylbromide also react with the β-carbon atom of the $\Delta^{1,10}$-dehydroquinolizidine enamine grouping (*201*).

When the immonium form of the enamine is precluded sterically, enamines are alkylated solely on the nitrogen atom. Methylation of neostrychnine with methyliodide proceeds in this manner as well as that of Δ^{5}-tetrahydrojulolidine (**117**) (*202*), which affords only the N-methylated product (**118**).



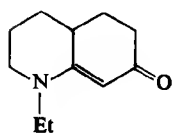
(117) **(118)**

An explanation of the exclusive N methylation of 1,2-dimethyl-Δ^{2}-piperideine by means of methyliodide is more difficult. Pyrrolines and piperideines which are not alkylated on the nitrogen atom afford only quaternary ammonium salts on alkylation (*203–205*), for example **119**.



(119)

Secondary enamino ketones such as $\Delta^{8,9}$-octahydro-7-quinolone (**64**) furnish a mixture of N- and C-alkylated bases, **120** and **121**, respectively, on treatment with ethyliodide (*168*). Alkylation of tertiary enamino ketones as, for example, **101** proceeds exclusively on the oxygen-atom, forming product **122** (*206*).



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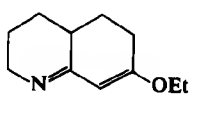

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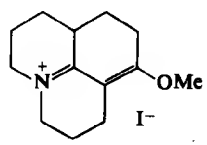
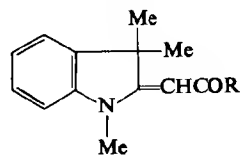


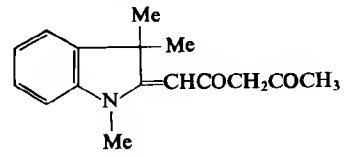
(122)

Acylation of heterocyclic enamines is to a great extent similar to alkylation, and usually occurs on the β-carbon atom of the enamine grouping.

Acylation of 1,3,3-trimethyl-2-methyleneindoline (**103**) leads upon basification to 1,3,3-trimethyl-2-acylmethyleneindoline (**123**) (*207*). Reaction with diketene affords the corresponding β-diketo compound **124**.

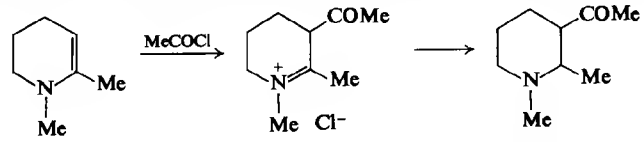


(123)



(124)

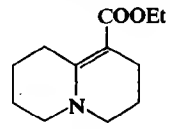
1,2-Dimethyl-3-acetylpiperidine (**125**) has been prepared by acetylation of 1,2-dimethyl-Δ^{2}-piperideine, followed by hydrogenation (Scheme 8) (*163*).



(125)

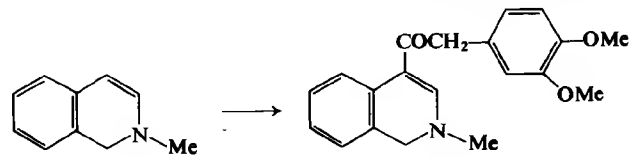
Scheme 8

Treatment of $\Delta^{1,10}$-dehydroquinolizidine with ethyl chloroformate furnishes upon basification 1-carbethoxy-$\Delta^{1,10}$-dehydroquinolizidine (**126**).



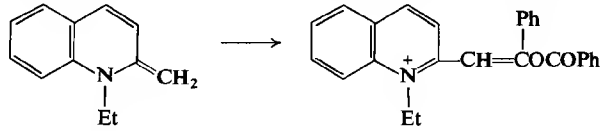
(126)

By acylation of 2-methyl-1,2-dihydroisoquinoline (**127**) with 3,4-dimethoxyphenacylchloride a C-4 alkylated product **128** is formed (*208*).



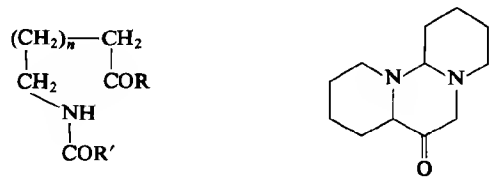
(127) **(128)**

A methylene base formed from quinaldine ethiodide, 1-ethyl-2-methylene-1,2-dihydroisoquinoline (**129**), exhibits a number of reactions characteristic of enamines (*207,209*). On treatment with benzoylchloride a dialkylated product (**130**) is produced by C and subsequent O benzoylation (*210*).



(**129**) (**130**)

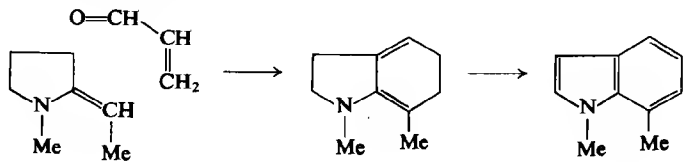
Reaction of 2-alkyl-Δ^1-pyrrolines and 2-alkyl-Δ^1-piperideines with acid chlorides leads to ring-opening and formation of N-acylated amino ketones (**131**, $n = 1, 2$) (*211–213*). Ketene reacts with Δ^1-piperideine to form a tricyclic derivative (**132**) (*214*).



(**131**) (**132**)

2. *Reactions of Heterocyclic Enamines with α,β-Unsaturated Compounds*

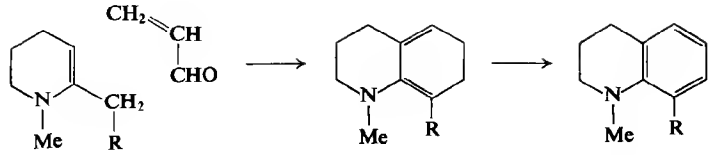
Enamines react readily with compounds containing a double bond activated by electronegative groups. Addition of acrolein to 1-methyl-2-ethylidenepyrrolidine, followed by dehydrogenation, leads to 1,7-dimethylindole (**133**) (Scheme 9) (*215*).



(**133**)

Scheme 9

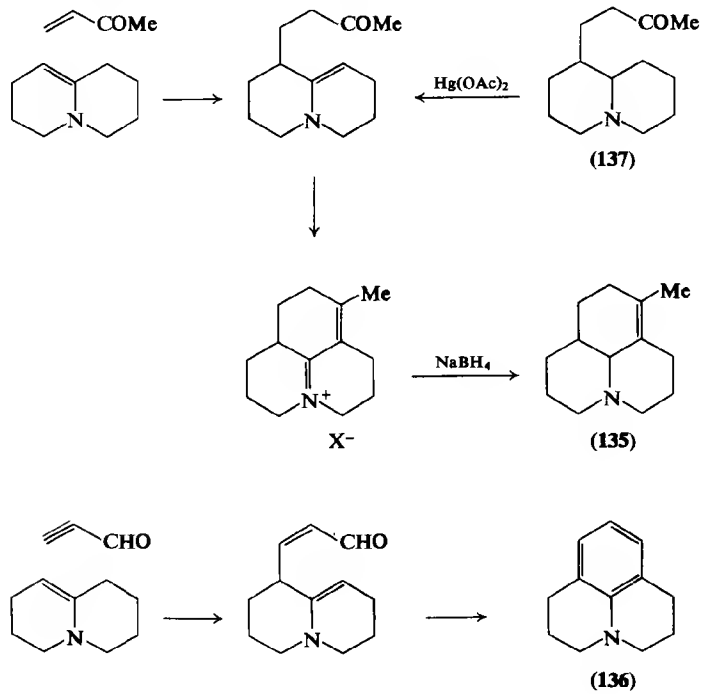
In a similar addition to 1-methyl-2-alkyl-Δ^2-piperideines, 1-methyl-8-alkyl-1,2,3,4-tetrahydroquinolines (**134**) were obtained (Scheme 10) (*163*).



(**134**)

Scheme 10

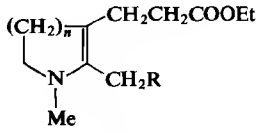
Bohlmann (*201*) reported the reaction of $\Delta^{1,10}$-dehydroquinolizidine with methyl vinyl ketone and with propargyl aldehyde forming a partially saturated derivative of julolidine **135** and julolidine (**136**), respectively. Compound **135** can be prepared also by mercuric acetate dehydrogenation of ketone **137**, which is formed by condensation of 1-bromoethylquinolizidine with ethyl acetoacetate (Scheme 11).



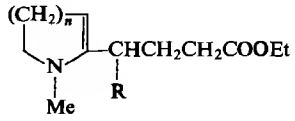
(**137**) (**135**) (**136**)

Scheme 11

The addition of ethyl acrylate to 1,2-dimethyl-Δ^2-piperideine (*163*), 1-methyl-2-ethyl-Δ^2-piperideinc (*164*), and 1,2-dimethyl-Δ^2-pyrrolidine (*216,217*) occurs, yielding both possible enamine structures (**138** and **139**, $n = 1, 2$).

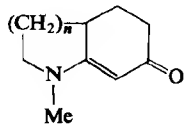


(138)

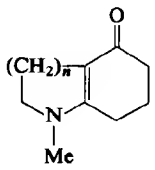


(139)

Addition to 1,2-dimethyl-Δ^2-piperideine or 1,2-dimethyl-Δ^2-pyrroline is followed by intramolecular alkylation by the ester group as a side reaction to give **140** and **141** ($n = 1, 2$), respectively. Cyclization products **142** and

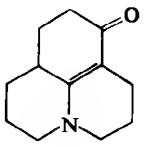


(140)

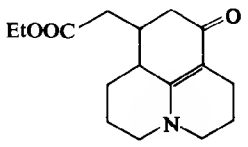


(141)

143 are the main products in the reaction of ethyl acrylate or ethyl glutaconate with $\Delta^{1,10}$-dehydroquinolizidine (*201*). On the other hand, the addition of butadiene carboxylic acid leads to a mixture of products (*218*).

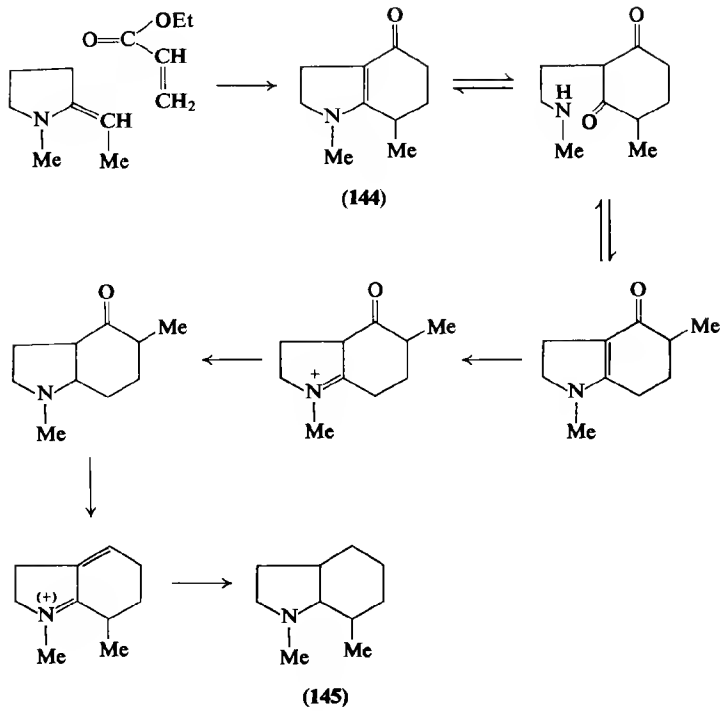


(142)



(143)

An interesting addition of ethyl acrylate has been reported in the case of 1-methyl-2-ethylidenepyrrolidine. An unsaturated amino ketone **144** is formed, which rearranges to 1,7-dimethyloctahydroindole (**145**) on reduction with formic acid, as established by dehydrogenation to 1,7-dimethylindole (Scheme 12) (*217*).

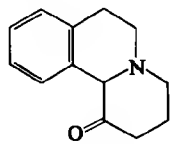


(144)

(145)

Scheme 12

Imines also react with α,β-unsaturated aldehydes or ketones (*219–221*). 3,4-Dihydroisoquinoline reacts, for example, with methyl vinyl ketone to give cyclic ketone **146** (*222,223*).

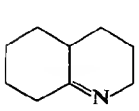


(146)

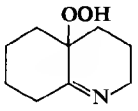
3. *Reactions of Heterocyclic Enamines with Other Electrophilic Reagents*

Enamines are generally very sensitive to oxidation (*92,224*). By standing in the air they become brown and afford an undefinable mass. Imines, by

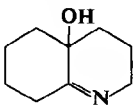
contrast, form hydroperoxides with atmospheric oxygen, which may be isolated (*151,225–229*). $\Delta^{1,9}$-Octahydroquinoline (**147**) affords a crystalline hydroperoxide (**148**), which may be reduced to 10-hydroxy-$\Delta^{1,9}$-octahydroquinoline (**149**), or hydrolyzed to a cyclic oxolactam (**150**). Reactions with many analogous compounds have been reported (*230–232*).



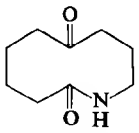
(147)



(148)

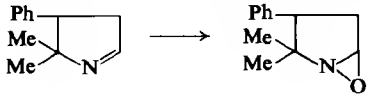


(149)



(150)

By means of perbenzoic acid oxidation, a bicyclic oxazirane (*233,234*) (**152**) is formed from 5,5-dimethyl-4-phenyl-Δ^1-pyrroline (**151**).

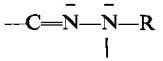


(151) (152)

Dibenzoylperoxide oxidation of $\Delta^{1,10}$-dehydroquinolizidine affords an immonium salt, which can be reduced with sodium borohydride to 1-benzoyloxyquinolizidine. Treatment of the salt with base liberates 1-benzoyloxy-$\Delta^{9,10}$-dehydroquinolizidine (*221*).

A dimer is formed by the action of hydrogen peroxide on the quaternary salt of 3,4-dihydroisoquinoline (*235*). The other similar reactions are of small importance.

The fact that 2-N-substituted pyrazolines containing a



grouping in the molecule react in a manner which is typical of enamines is very interesting (*236*).

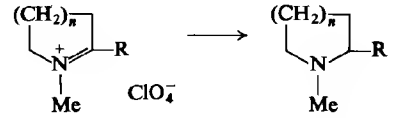
B. Reactions of Enamine Salts with Nucleophilic Reagents

Reactions at the carbon–nitrogen double bond of iminium salts are analogous to nucleophilic reactions at the carbonyl group of aldehydes and ketones. This is why free enamines do not react with nucleophilic reagents, whereas their salts can undergo such reactions.

1. *Reduction*

Tertiary heterocyclic enamines are reduced with metals in acidic media (*142*) or electrolytically (*237,238*) and their salts are reduced with lithium aluminum hydride or sodium borohydride (*239,240*) to the corresponding saturated amines.

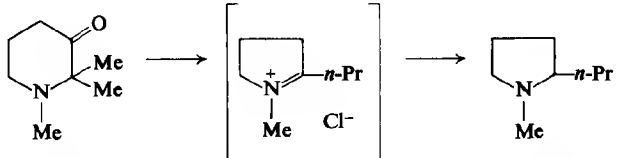
Reduction of 1-methyl-2-alkyl-Δ^1-pyrroline and 1-methyl-2-alkyl-Δ^1-piperideine perchlorates with complex hydrides prepared in situ by partial decomposition of lithium aluminum hydride with the optically active alcohols (–)-menthol and (–)-borneol affords partially optically active 1-methyl-2-alkyl pyrrolidines (**153**, $n = 1$) and 1-methyl-2-alkyl piperideines (**153**, $n = 2$), respectively (*241,242*).



(153)

$\Delta^{1,10}$-Dehydroquinolizidine reacts with the enantiomeric (–)- and (+)-menthyl chloroformates forming (–)- and (+)-menthoxycarbonyl-$\Delta^{1,10}$-dehydroquinolizidines. These can be reduced as such or in the form of their immonium salts with sodium borohydride to (–)- and (+)-1-menthoxycarbonylquinolizidines, which give (+)- and (–)-lupinin, respectively, on reduction with lithium aluminum hydride (*243*). The optical yield of the asymmetric reduction is about 10%.

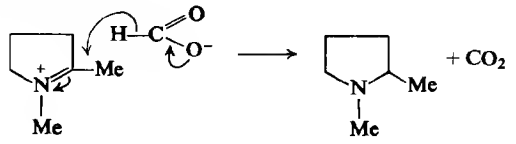
The intermediate formation of iminium salts is postulated in the reduction of α-amino ketones by the Clemmensen method, occurring with concomitant ring enlargement or contraction (*244–246*). Reduction of 1,2,2-trimethyl-3-piperidone (**154**) in this manner gave 1-methyl-2-isopropylpyrrolidine (**155**).



(154) (155)

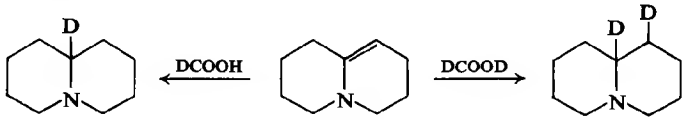
Enamines are also reduced with formic acid (*247*). Distillation of 1,2-dimethyl-Δ^1-pyrroline formate (**156**) affords 1,2-dimethylpyrrolidine (*248*). The reaction is usually carried out by heating of the enamine salt with

formic acid. Potassium formate can be added to increase the temperature of the reaction mixture.



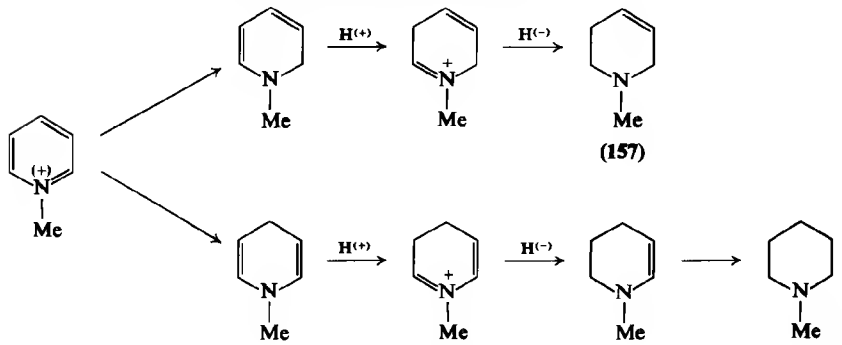
(156)

This method has been used for the reduction of 1-methyl-2-alkyl-Δ^1-pyrrolinium and 1-methyl-2-alkyl-Δ^1-piperideinium salts by Lukeš et al. (*42,249–251*) and for the reduction of more complex bases containing the dehydroquinolizidine skeleton by Leonard et al. (*252*). The formic acid reduction may be satisfactorily explained by addition of a hydride ion, or an equivalent particle formed from the formate anion, to the β-carbon atom of the enamine (*253*), as shown in Scheme 13.



Scheme 13

1,2-Dihydro- and 1,4-dihydro derivatives are formed as intermediates in the reduction of quaternary pyridine salts and their homologues with sodium borohydride or formic acid. A proton is added to the present enamine grouping and the formed immonium salts are reduced to the 1-methyl-1,2,5,6-tetrahydropyridine derivatives (**157**) and to completely saturated compounds (**158**) (*254*) (Scheme 14).

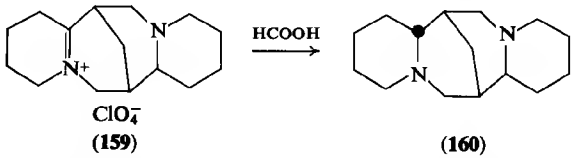


(157)

(158)

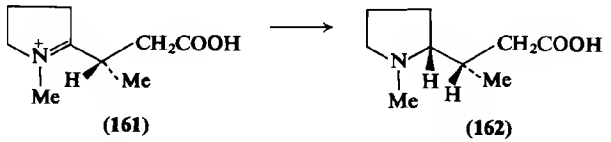
Scheme 14

The formic acid reduction has great stereospecificity. Reduction of (−)-Δ^5-dehydrosparteine (**159**) and (−)-$\Delta^{5,11}$-didehydrosparteine affords (−)-sparteine (**160**) and (−)-α-isosparteine, respectively (*252*).



(159) (160)

Reduction of the quaternary immonium salt **161**, obtained by treatment of 1-methyl-2-ethylidenepyrrolidine with ethyl bromoacetate, by means of either sodium borohydride or formic acid, leads to (−)-erythro-2-(2-N-methylpyrrolidyl)butyric acid (**162**), in agreement with Cram's rule (*196*).

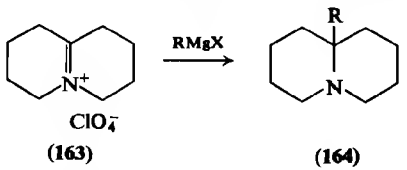


(161) (162)

In both cases, the hydride ion approaches the double bond from the sterically more accessible side of the molecule. Reduction of imines by metals and acids, electrolytically or by formic acid gives saturated secondary amines (*38,255*).

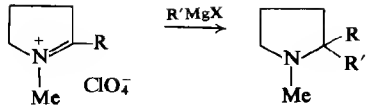
2. *Reactions of Enamine Salts with Organometallic Compounds*

Organolithium and organomagnesium compounds react with enamine salts to give amines substituted on the α-carbon atoms. The treatment of $\Delta^{5,10}$-dehydroquinolizidinium perchlorate (**163**) with alkylmagnesium halides gives 9-alkylated quinolizidines (**164**) (*252,256*). Formation of



(163) (164)

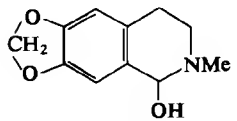
1-methyl-2,2-dialkylpyrrolidines (**165**) has been observed on treatment of 1-methyl-2-alkyl-Δ^1-pyrrolinium perchlorates with alkylmagnesium halides (*257*).



(165)

Δ^1-Pyrrolines and Δ^1-piperideines do not generally react with Grignard reagents (*149,258*). The addition complex reverts to the starting amine when treated with water during the hydrolysis step. In some cases the Grignard reagent causes proton removal. This is followed by condensation of the anion thus formed with a second molecule of the Δ^1-pyrroline (*255*).

The alkaloids cotarnine (*259*), hydrastinine (*261*), and berberinal (*260*), each possessing a grouping formed by interaction of an aldehyde with a secondary amino group in their molecule, are unusual. The Grignard reaction of free base **166** does not occur as readily as that of the corresponding salt **167**. Both reactions lead to the alkylated product **168**. For example, only 50% of hydrastinine reacts and 50% is regenerated, whereas hydrastinine hydrochloride reacts almost quantitatively (*261*). The salt undoubtedly contains a C=N double bond. In the case of the free base, the presence of a C=N double bond was not proven, and the reaction probably occurs by direct cleavage of the C—OH bond.



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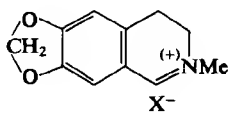

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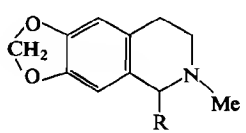
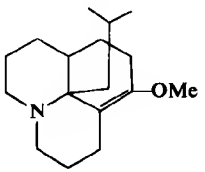


(168)

Reaction of organometallic compounds with enamine salts have been successfully used for the synthesis of some natural products (*256*). Thus reaction of the immonium salt of O-alkylated enamino ketone **122** with isobutyllithium affords the compound **169**.



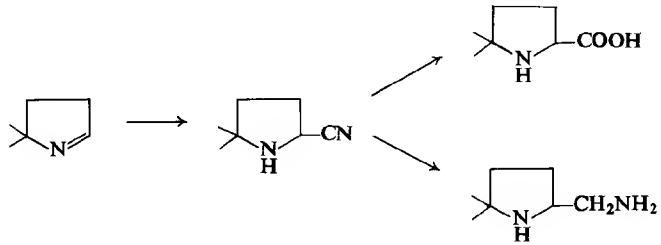
(169)

3. *Reactions of Enamine Salts with Other Nucleophilic Reagents*

Enamine salts react with many nucleophilic reagents. The reaction with the cyanide ion is noteworthy. 1-Methyl-2-ethyl-2-cyanopyrrolidine (**170**) is formed on treatment of alkali cyanide with 1-methyl-2-ethyl-Δ^1-pyrrolinium perchlorate (*242*). The reduction of the tertiary nitrile (**170**) with

(170)

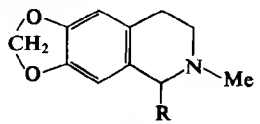
lithium aluminum hydride in ether gives 1-methyl-2-ethylpyrrolidine. Hydrogen cyanide can be removed by treatment with acids with re-formation of 1-methyl-2-ethyl-Δ^1-pyrrolinium salts. On the other hand, addition of hydrogen cyanide to Δ^1-pyrrolines yields stable nitriles, which can be easily saponified to acids or reduced to amines (*255*) (Scheme 15).



Scheme 15

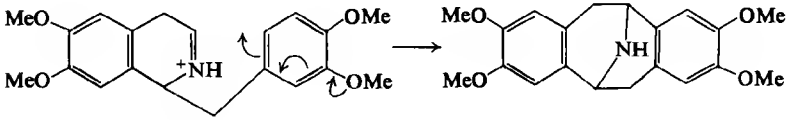
Δ^1-Pyrroline-N-oxides when unsubstituted in the 2 position readily add hydrogen cyanide. The 1-hydroxy-2-cyanopyrrolidines thus formed undergo oxidation to 2-cyano-Δ^1-pyrroline-N-oxides.

Treatment of cotarnine and similar compounds with hydrogen cyanide, alkoxides, mercaptides, hydroxylamine, hydrazine, and amines has been reported to give 1-substituted derivatives of 1,2,3-tetrahydroisoquinoline (**171**, R = CN, OR, SP, NHOH, $NHNH_2$, NHR) (*262–265*).



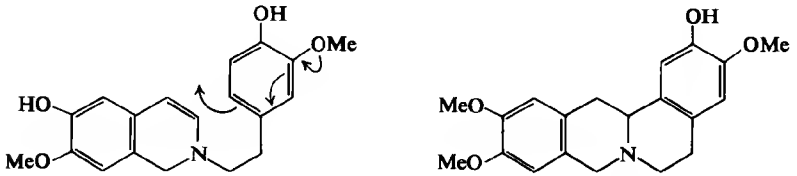
(171)

The cyclization reaction of some substituted 1,2-dihydroisoquinolines is of interest (*266*). The reduction of papaverine with tin and hydrochloric acid affords the 1,2-dihydro compound in the form of immonium salt **172**, which then undergoes a cyclization reaction in the acidic medium to give compound **173**, called pavine (*267*).



(172) **(173)**

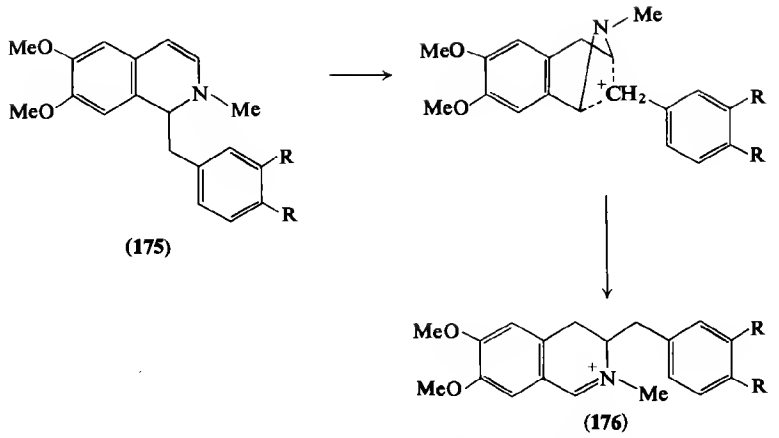
On treatment of N-methylpapaverine, formed by the lithium aluminum hydride reduction of papaverine methiodide with phosphoric acid, N-methylpavine is formed which is identical with the racemic alkaloid argemonine. This reaction was used for the synthesis of the alkaloid (+)-coreximine (*268*) (**174**) and similar compounds containing the proto-berberine grouping in the molecule (*269,270*).



(174)

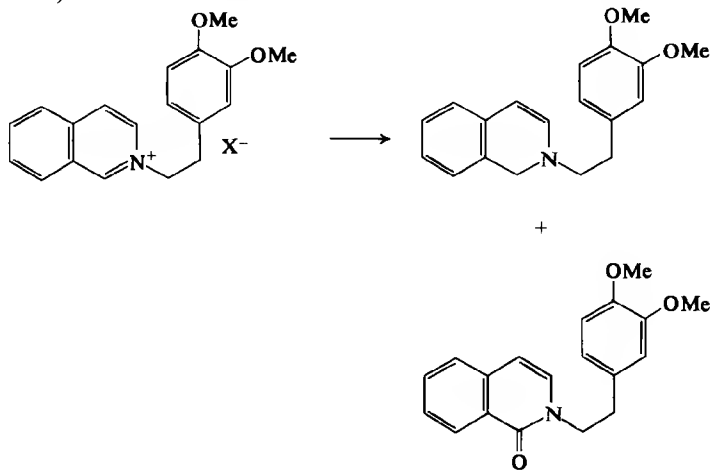
Knabe et al. (*271–274*) later observed that 6,7-dimethoxy-2-methyl-1,2-dihydroisoquinolines (**175**), possessing either a free or a substituted benzyl group in position 1, readily rearrange to 3,4-dihydroisoquinoline salts (**176**) on treatment with dilute acids.

2-Methyl-1,2-dihydropapaverine (**175**, R = OMe) rearranges to the 2-methyl-3-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium salt (**176**, R = OMe) under very mild conditions (treatment with 2% hydrochloric acid). A similar rearrangement of 1-(3,4-methylenedioxybenzyl)-2-methyl-6,7-dimethoxyisoquinoline (**175**, R, R = —O—CH_2—O—) affords 3-(3,4-methylenedioxybenzyl)-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium chloride (**176**, R, R = O—CH_2—O—) (*266*). The reaction was shown to be an allylic rearrangement with internal return (*275,276*).



(175) **(176)**

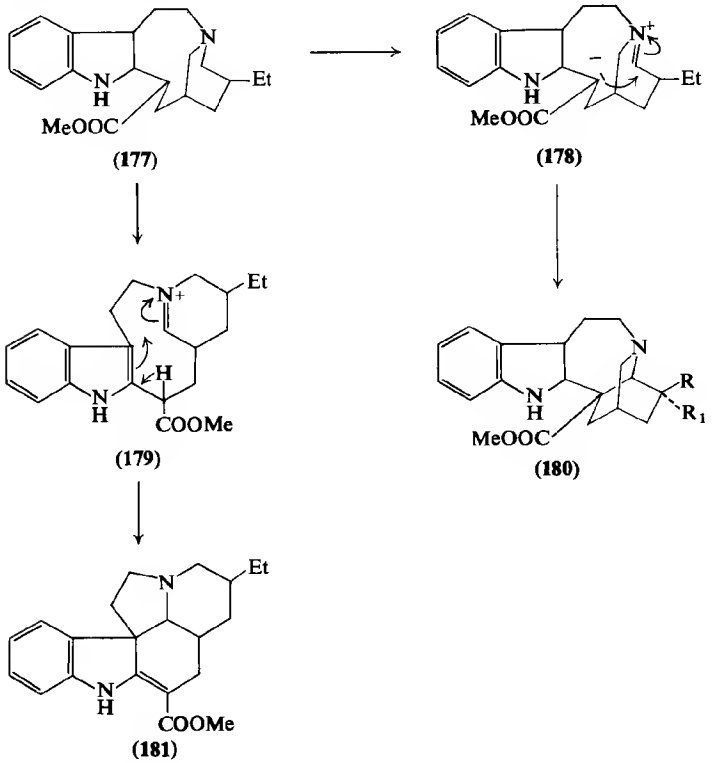
The disproportionation reaction of isoquinolinium salts to 1,2-dihydroisoquinolines and isocarbostyril derivatives (Scheme 16) was used by Brown and Dyke for the synthesis of berberine and 8-oxoberberine derivatives (*277–279*).



Scheme 16

The mercuric acetate dehydrogenation of carbomethoxydihydrocleavacine (**177**) yields immonium salt **178**, which undergoes transannular cyclization to give a mixture of coronaridine (**180**, R = Et, R_1 = H) and dihydrocantharanthine (**180**, R = H, R_1 = Et). The reaction is accompanied

by a similar cyclization (*280*) to the β position of the indole nucleus forming compound **181** via **179**.



From the preparative point of view, reactions of heterocyclic aromatic compounds with nucleophilic reagents are very important, especially the reactions of their quaternary salts containing a formal enamine grouping in the molecule.

With pyridine derivatives and compounds containing the pyridine ring, some reactions are of particular interest (*113,285,286*): reaction with organometallic compounds (*281*) (organomagnesium or organolithium), reduction with sodium in ethanol, with complex hydrides or formic acid and reactions with hydroxyl or cyanide ions (*282–284*) and with some organic compounds containing the reactive methylene group. The N-oxides of these heterocyclic bases (*287,288*), especially their quaternary salts, react in a similar manner (*289,290*).

V. Aldol Reactions of Heterocyclic Enamines and Their Importance for the Biosynthesis of Alkaloids

The successful determination of the structure and stereochemistry of alkaloids, followed by their unequivocal synthesis, is not the only goal of organic chemists studying these natural products. The importance of solving the problem of their biogenesis in living organisms, of defining their relation to other compounds in the organism, and at the same time of getting acquainted with their importance for the plant is now becoming more apparent.

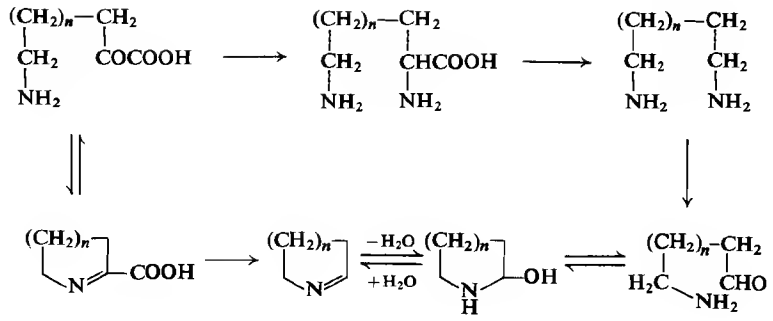
The first step in this study has involved experiments which synthesize alkaloids in vitro under quasi-cellular conditions, using reactions which can proceed in the living cell and compounds which actually occur in the cell or which are supposed to be intermediates in the plant metabolism. Such syntheses are designated as syntheses under "physiological conditions."

Aldol reactions of enamines with reactive methylene groups constitute the basic step in the Robinson theory of alkaloid biogenesis. The theory has been modified by Schöpf, Woodward, Wenkert, and other chemists. Thanks to their studies we can obtain a satisfactory image of the biogenesis even of some very complex alkaloids. In the synthesis of alkaloids, two main groups of reactions take part: degradation reactions of amino acids or sugars to give starting materials, and synthetic processes proceeding in the cell to form these alkaloids.

Heterocyclic enamines Δ^1-pyrroline and Δ^1-piperideine are the precursors of compounds containing the pyrrolidine or piperidine rings in the molecule. Such compounds and their N-methylated analogs are believed to originate from arginine and lysine (*291*) by metabolic conversion. Under cellular conditions the proper reaction with an active methylene compound proceeds via an aldehyde ammonia, which is in equilibrium with other possible tautomeric forms. It is necessary to admit the involvement of the corresponding α-ketoacid (*12,292*) instead of an enamine. The α-ketoacid constitutes an intermediate state in the degradation of an amino acid to an aldehyde. α-Ketoacids or suitably substituted aromatic compounds may function as components in active methylene reactions (Scheme 17).

The synthetic process proceeding under physiological conditions can be imitated in vitro with the object of establishing the validity of biogenetic hypotheses (*293*) as well as finding new potential routes for the synthesis of pharmaceuticals (*294*).

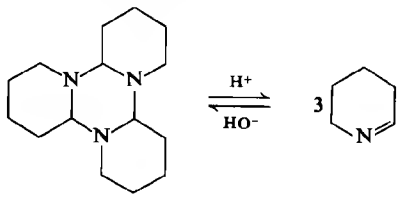
The aldol reactions of enamines may be formally considered to proceed via acyclic amino aldehyde or amino ketone forms, in spite of the fact that the cyclic enamine forms can also take part in aldol reactions.



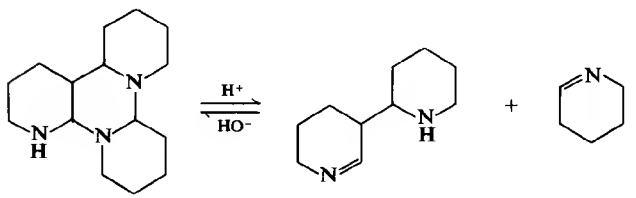
$n = 1,2$

Scheme 17

The simplest compounds, Δ^1-pyrroline and Δ^1-piperideine, do not exist in the monomeric form. Schöpf et al. (*295*) described two geometric isomers of Δ^1-piperideine trimer and called them α- and β-tripiperideines (**182**). An equilibrium exists between Δ^1-piperideine and both trimers which, therefore, react as typical aldehyde ammonia. The trimer rearranges at pH 9–10 in an almost quantitative yield to isotripiperideine (**183**) which, in turn, is in equilibrium with tetrahydroanabasine (**184**) and Δ^1-piperideine.



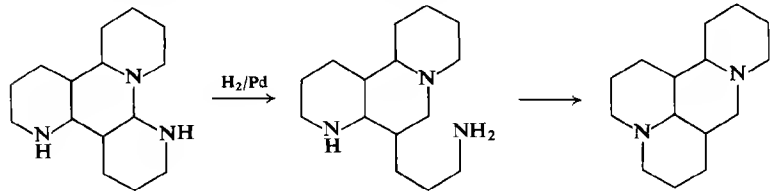
(**182**)



(**183**) (**184**)

Isotripiperideine and α-tripiperideine structures differ from each other in a new C—C bond formed in is otripiperideine by an aldol reaction (*296, 297*). In aqueous media at pH 2–13, two molecules of Δ^1-piperideine yield tetrahydroanabasine (*297*).

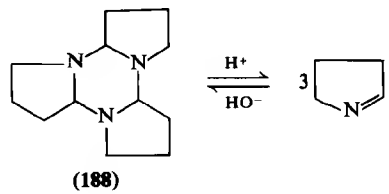
The last isomer, the so-called aldotripiperideine (**185**), is obtained by the action of acid catalysts on α-tripiperideine at its boiling point (*298,299*), or in aqueous solution at pH 9.2 and 100°C. Further aldol reaction between tetrahydroanabasine and Δ^1-piperideine obviously occurs. Hydrogenolysis of this compound gives dihydroaldotripiperideine (**186**) which is convertible into matridine (**187**), a reduction product of the alkaloid matrine.



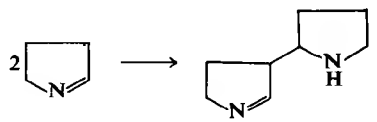
(**185**) (**186**) (**187**)

Curiously, neither Δ^1-piperideine nor tetrahydroanabasine undergo aldolization in strongly acidic or strongly alkaline media; the reaction occurs only at pH 2–13, when both the free base and its salt are present (*295*). This relation between the rate of aldolization and pH indicates that aldolization occurs by condensation of the methylene group of the immonium salt with the free base.

Δ^1-Pyrroline affords a trimer (*300*), tripyrroline (*188*). In the five-membered series, only 3-(2-pyrrolidyl)-Δ^1-pyrroline (**189**), a dimeric aldolization product, was always obtained under the reaction conditions causing the formation of isotripiperideine or even aldotripiperidine in the six-membered series. Product **189** can be prepared by allowing an aqueous solution of pyrroline to stand at pH 7.



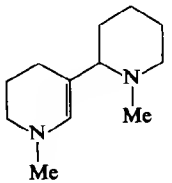
(**188**)



(**189**)

Condensation of Δ^1-pyrroline with pyrrole readily affords 2-(2-pyrrolidyl)pyrrole (*82*). The dimerizations of some derivatives of Δ^1-piperideine, e.g., Δ^1-pyrroline and Δ^1-piperideine-2-carboxylic acids, take a similar course (*301*).

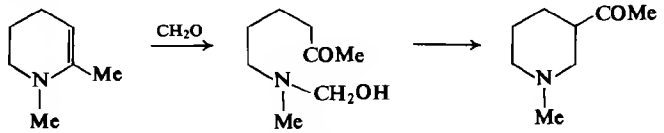
The N-substituted bases also undergo dimerization when the 2 position is free. Reduction of N-substituted five- and six-membered lactams and imides with various reducing reagents gives rise to various amounts of higher boiling bases. Recently, it has been found that these are dimerization products of intermediate 1-alkyl-Δ^2-pyrrolines and 1-alkyl piperideines (*131*). Thus, for example, 3-(1,2-dimethylpiperidyl)-1-methylpiperideine, i.e., N,N'-dimethyl-Δ^2-tetrahydroanabasine (**190**), is formed by reduction of 1-methyl-2-piperidone with sodium in ethanol. The same dimer was later obtained by Leonard and Hauck (*1*) on dehydrogenation of N-methylpiperidine with mercuric acetate, and by Schöpf on partial hydrogenation of the N-methylpyridinium salts.



(190)

The only stable monomeric form of 1-methyl-Δ^2-piperideine is as the immonium salt.

The dimer of 1-methyl-Δ^2-pyrroline (**39**) was obtained by reduction of N-methylpyrrole with zinc and hydrochloric acid (*132*) and, together with the trimer, by mercuric acetate dehydrogenation of N-methylpyrrolidine (*131*). Δ^1-Pyrroline-N-oxides form dimers in a similar manner (*302*). Treatment of 1,2-dimethyl-Δ^2-piperideine with formaldehyde, producing 1-methyl-3-acetylpiperidine (*603*), serves as an example of a mixed aldol reaction (Scheme 18).

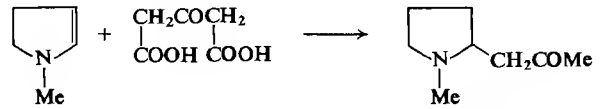


Scheme 18

The synthesis of some simple alkaloids under so-called physiological conditions has been made possible by the development of methods of

preparation of Δ^1-pyrroline, Δ^1-piperideine, and their N-methyl derivatives and by knowledge of their basic conversions.

Anet et al. (*304*) obtained in 1947 the alkaloids hygrine (**191**) and kuskhygrine (**192**) in a very good yield by treatment of γ-methylaminobutyraldehyde with acetoacetic or acetonedicarboxylic acids at pH 7. The same reaction was later accomplished by Galinovsky et al. (*305–307*), who prepared the starting aldehyde by partial reduction of 1-methyl-2-pyrrolidone with lithium aluminum hydride. He used acetonedicarboxylic acid for the synthesis of both alkaloids and showed that a mixture of both alkaloids is formed, the composition of which depends on the ratio of components.



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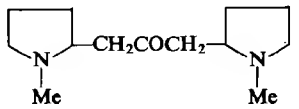
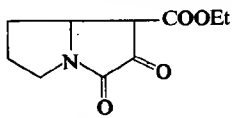


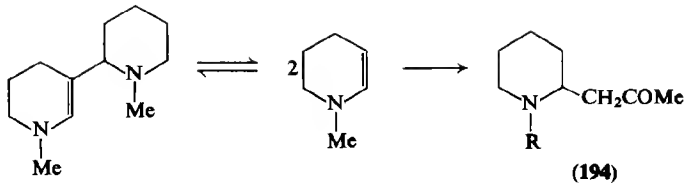
(192)

Norhygrine has been prepared by Schöpf from Δ^1-pyrroline. Goldschmidt (*308*) synthesized 1-carbethoxy-2,3-dioxopyrrolizidine (**193**) by condensation of Δ^1-pyrroline with diethylester of oxosuccinic acid.



(193)

In the six-membered series the alkaloids of *Punica granatum*, isopelletierine and methylisopelletierine, have been obtained by treatment of enamines with acetoacetic acid. Isopelletierine (**194**, R = H) was prepared also by Schöpf et al. from Δ^1-piperideine (*309–311*). The reversibility of aldol dimerization (*124,131*) of enamines has been established by the synthesis of methylisopelletierine (**194**, R = Me) from dimethyltetrahydroanabasine, accomplished by Lukeš and Kovář (*101*) (Scheme 19).

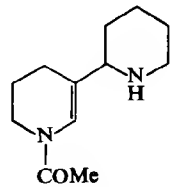


(194)

Scheme 19

The acetylation of isotripiperideine by means of a ketone in nonpolar media affords a compound which decomposes in acidic media to Δ^1-piperideine and a monoacetyl derivative of the enamine form of tetrahydroanabasine (**195**). This monoacetyl derivative is identical with the alkaloid amodendrine (*312*). A similar acylation with cinnamoylchloride affords the alkaloid orensine (**196**) (*313*), the optically active form of which is the natural alkaloid adenocarpine (*314*). The hydrolysis of alkaloid santiaguine gives α-truxilic acid (*314*).

From a vast number of alkaloids containing the Δ^1-pyrroline or Δ^1-piperideine ring in the molecule, alkaloids myosmine (**197**) and lobinaline (*315*) (**198**) of *Lobelia cardinalis* L. may be mentioned.



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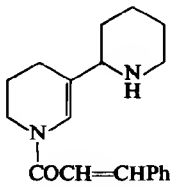

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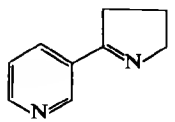
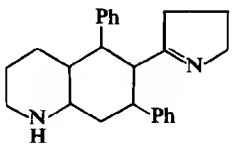
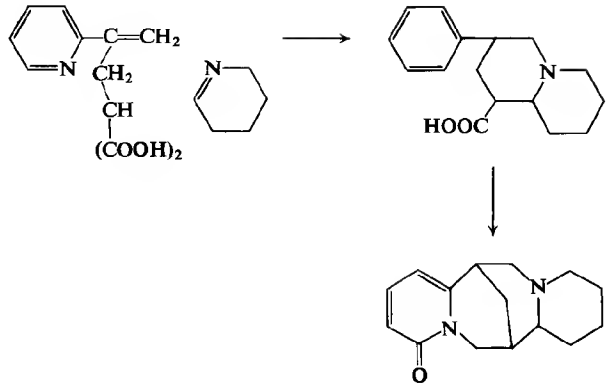




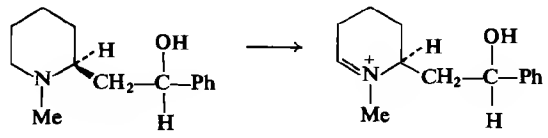
(198)

The reaction of 2-(α-pyridyl)alkylmalonic acid with Δ^1-piperideine leading to formation of 3-(α-pyridyl)quinolizidine-1-carboxylic acid on decarboxylation, has been used by Van Tamelen and Foltz (*316*) for the syntheis of the alkaloid lupanine (Scheme 20). A very elegant synthesis of matrine has been accomplished by Bohlmann et al. (*317*).

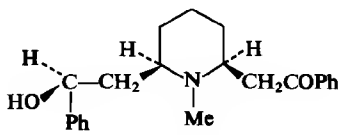


Scheme 20

The alkaloid sedamine has been prepared under physiological conditions too (*318*). Aldolization of the immonium salt **200**, obtained by mercuric acetate dehydrogenation of (2S,8R)-(−)-sedamine (**199**), with benzoylacetic acid produces (2S,6R,8S)-(−)-8,10-diphenyllobelinol (i.e., (−)-lobeline) (**201**). This determines its absolute configuration (*319*, *320*).

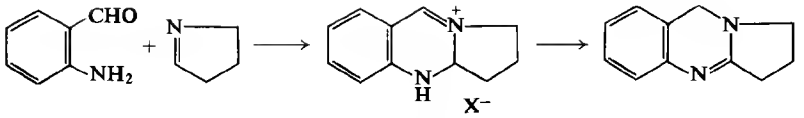


(199) (200)



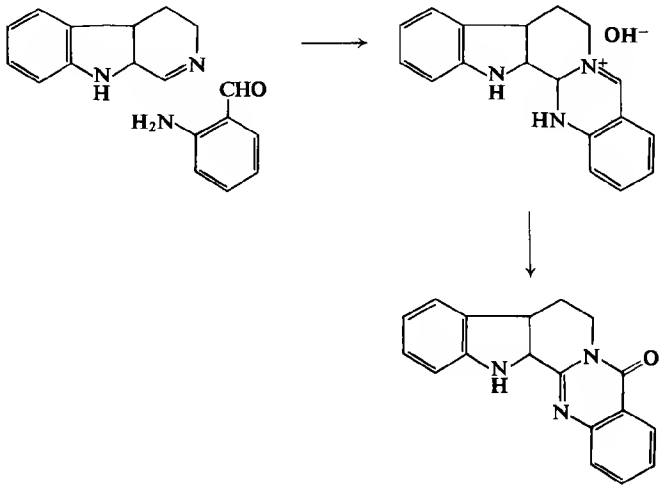
(201)

Condensation of Δ^1-pyrroline with *o*-aminobenzaldehyde leads to dihydroquinazolinium salt **202** on acidification, which in turn can be reduced to desoxyvasicine (**203**).



(202) (203)

The synthesis of alkaloids from dihydronorharmane, condensation of which with *o*-aminobenzaldehyde gives rutaecarpine (**204**) (*321–323*), is of a particular interest.

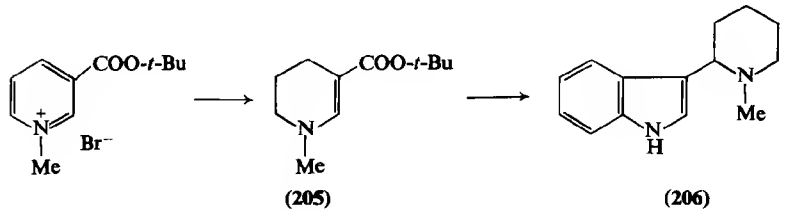


(204)

All heterocyclic enamines readily undergo condensation with *o*-aminobenzaldehyde. The quinoxaline derivatives thus formed have a characteristic yellow color. Therefore, this reaction can serve as evidence of the presence of an enamine in plants (*295,309*).

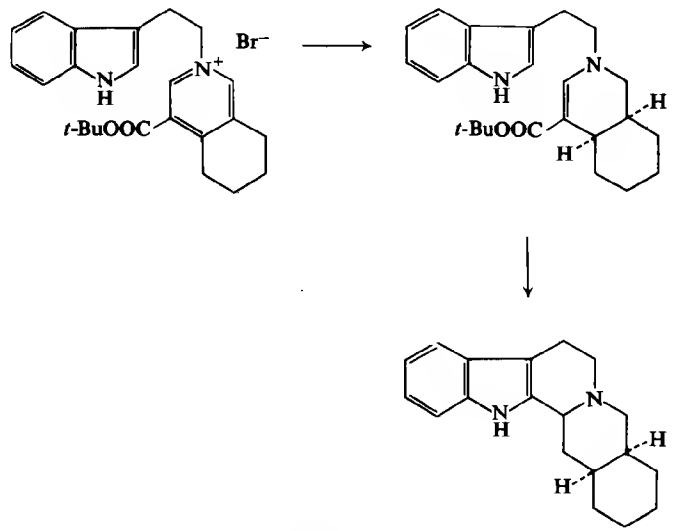
A characteristic of all the above reactions is that the yield of the aldolization product depends on the pH of the reaction mixture (*324*), the maximum yield usually occurring near pH 7. Such reactions have been carried out in vitro in dilute aqueous buffer under so-called physiological conditions, i.e., conditions attainable in the living cell. Although this oversimplified technique for the study of alkaloid biogenesis is now being abandoned in favor of experiments in vivo with labeled precursors, such reactions are still of interest to organic chemists.

Partial hydrogenation of the quaternary pyridinium salts in the presence of triethylamine on palladium in methanol has been used for the synthesis of a large number of alkaloids. The tetrahydropyridine derivatives thus formed undergo various cyclization reactions in acidic media (*89*).



(205) (206)

Hydrogenation of *t*-butyl nicotinate methobromide, followed by hydrolysis of the 1-methyl-3-tert-butoxycarbonyl-1,4,5,6-tetrahydropyridine product (**205**) in the presence of indole affords, on decarboxylation, the β-substituted derivative (**206**) (*325*). The formation of



Scheme 21

compounds containing the β-carboline grouping in the molecule takes a similar course (*90,326,327*) (Scheme 21).

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8

ENAMINES IN ORGANIC SYNTHESIS

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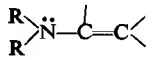
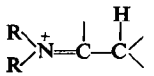
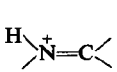
I. Introduction

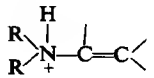
In this presentation, the following nomenclature will be used for commonly occurring functional groups:


enamine

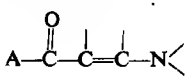

imine


corresponding imonium salt


corresponding iminium salt


corresponding amonium salt

Spelling of *amonium*, *imonium*, and *iminium* indicates derivation from amine and imine onium salts.



vinylogous amide A = H, alkyl
vinylogous urethane A = O-alkyl
vinylogous urea A = amine

In 1954 an intensive exploration of enamine chemistry got under way with Stork's appreciation and use of the tremendous potential of enamines for electrophilic substitution reactions (*1,2*). While the vinylamine functional group and its nucleophilic character were long known and simple methods were available for generating this system, its use as a synthetic principle in organic chemistry had not developed. However, with the recognition of enamines as activating derivatives for the nucleophilic α substitution of aldehydes and ketones, a universal interest was awakened. From the onset it seemed clear that gentler (less basic) reaction conditions and the possibility of controlled monosubstitution of enamines would give these compounds a synthetic advantage over enolate anions derived from the same carbonyl parents.

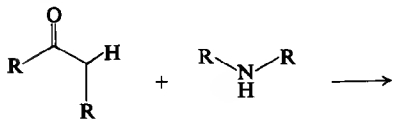
The bulk of enamine studies since Stork's original publication have focused on establishing the breadth and limitations of individual substitution reactions and on extending the list of useful electrophiles. In addition, auxiliary studies have enriched our knowledge about the ambident nature of the vinyl nitrogen system, stereoelectronic factors governing its reactivity, its stability and spectroscopic properties. An increasing number of synthetic applications of these fundamental studies can be expected in future years.

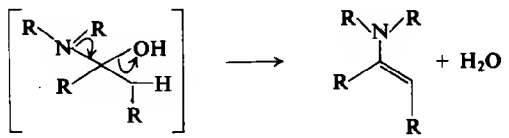
It is hoped that this chapter will be stimulating and helpful to those interested in synthetic applications of enamines. Thus the amount of discussion has been held at a minimum so that a maximum of variety and information could be presented in the form of examples, which may be useful as analogues in the solution of synthetic problems.

II. Formation of Enamines

A. Conversion of Aldehydes and Ketones to Enamines

The synthetic utility of enamines presupposes their general accessibility. In most cases, ketones are readily converted to enamines by condensation of the carbonyl compound with a secondary amine such as pyrrolidine, morpholine, or piperidine and azeotropic removal of water with a solvent such as benzene (*3–19*).

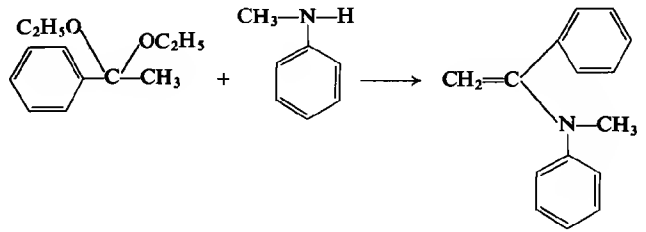




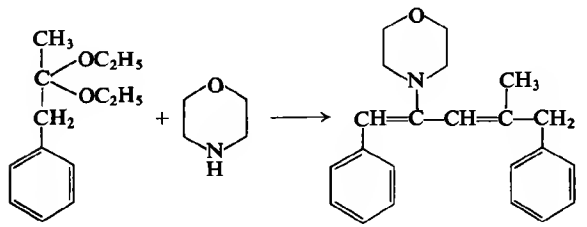
Enamines formed in this way may be distilled or used in situ. The ease of formation of the enamine depends on the structure of the secondary amine as well as the structure of the ketone. Thus pyrrolidine reacts faster than morpholine or piperidine, as expected from a rate-controlling transition state with imonium character. Six-membered ring ketones without α substituents form pyrrolidine enamines even at room temperature in methanol (*20*), and morpholine enamines are generated in cold acetic acid (*21*), but α-alkylcyclohexanones, cycloheptanone, and linear ketones react less readily. In such examples acid catalysis with *p*-toluenesulfonic acid or

benzoic acid, elevated temperatures such as from refluxing toluene or xylene, and the percolation of the refluxing solvent through a drying agent such as a molecular sieve, calcium hydride, or calcium carbide, have been found useful. More hindered ketones such as 2,6-dimethylcyclohexanone, 2,2-dimethylcyclohexanone, and spiro-2,2-tetramethylenecyclohexanone could not be converted to enamines by the azeotropic removal of water (*22*), and aliphatic methyl ketones tend to undergo self-condensation under these conditions. Even the use of a diethylketal (*23,24*) does not prevent this dimerization.

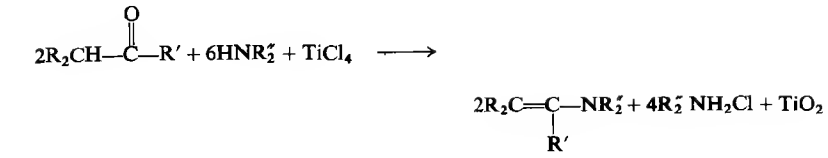
Some success in the generation of enamines from methyl ketones was found in the circuitous routes to enamines described below. A number of more recent methods for generation of enamines at low temperatures may



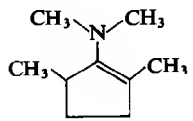
but:

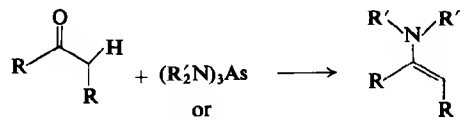


become useful in examples that are refractory to the azeotropic method. Thus the use of titanium tetrachloride (*25*) at 0–10°, with generation of titanium dioxide and an imonium salt corresponding to the enamine, has been described. In addition, tetradimethylamino titanium (*26*), tridialkylamino arsenic (*26,27*), and tridialkylamino boron compounds (*28*) have been used for enamine generation. For the reactions of ketones with dimethylamine or diethylamine, the addition of cupric chloride has been found advantageous in enamine formation (*29*).

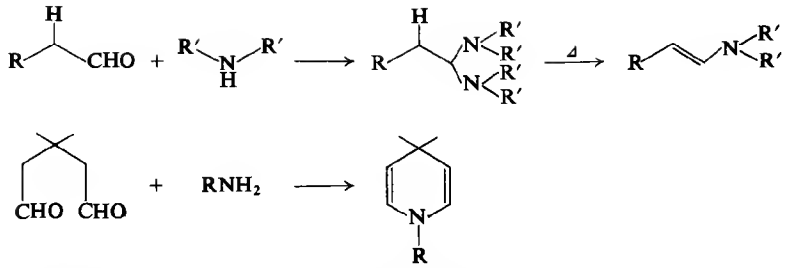


Enamine

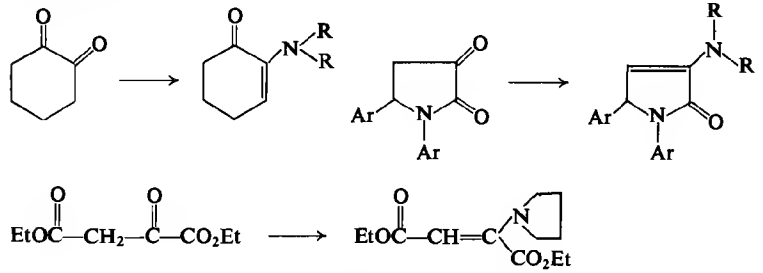
R	R′	R_2''	Yield, %
H	$CH(CH_3)_2$	$(CH_3)_2$	57
H CH_3	$CH(CH_3)_2$ CH_3	$-CH_2CH_2OCH_2CH_2-$	55
CH_3	C_6H_5	$-(CH_2)_4-$	62
CH_3	$CH(CH_3)_2$	$(CH_3)_2$	72
			86



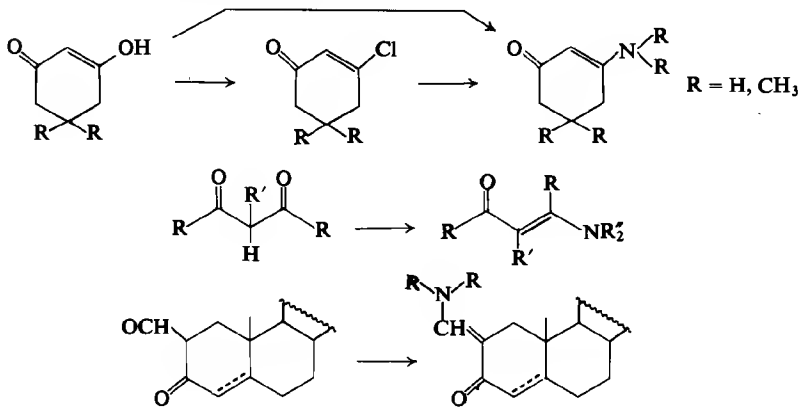
Enamines derived from aldehydes can usually be obtained by the reaction of 2 equivalents of a secondary amine with the carbonyl compound, in the presence of anhydrous potassium carbonate, followed by pyrolytic distillation of the aminal with elimination of one of the amine groups (*10,15, 30–36*). Ketones are directly converted to enamines under the conditions of aminal formation. The azeotropic removal of water with excess aldehyde has also been described (*32,37*).

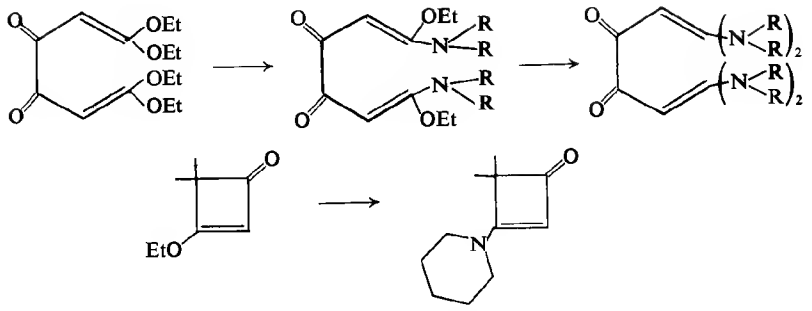


α-Dicarbonyl compounds are readily converted to enamino carbonyl compounds. Thus cyclohexane 1,2-dione (*38*), diethyloxaloacetate (*22*), and 3-ketopyrrolidones (*39,40*) were converted to enamines under dehydrating conditions.

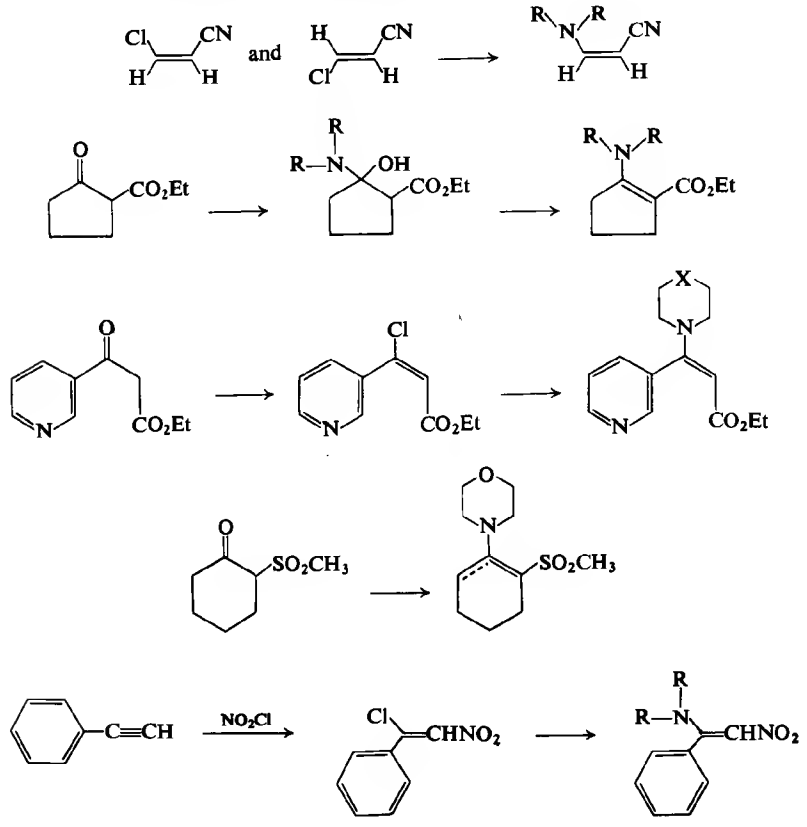


Enamines in which the vinyl nitrogen system is in conjugation with another functional group can be obtained from reactions of secondary amines with β-ketoaldehydes and β-diketones or their monoenol ether or vinyl halide derivatives (*41–46*).

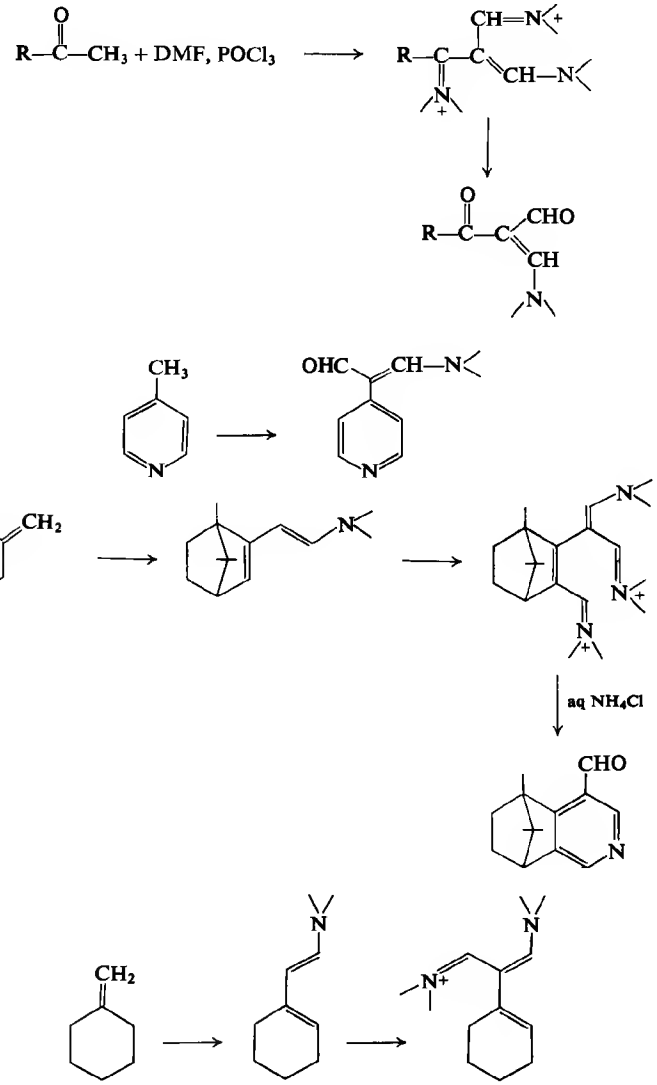




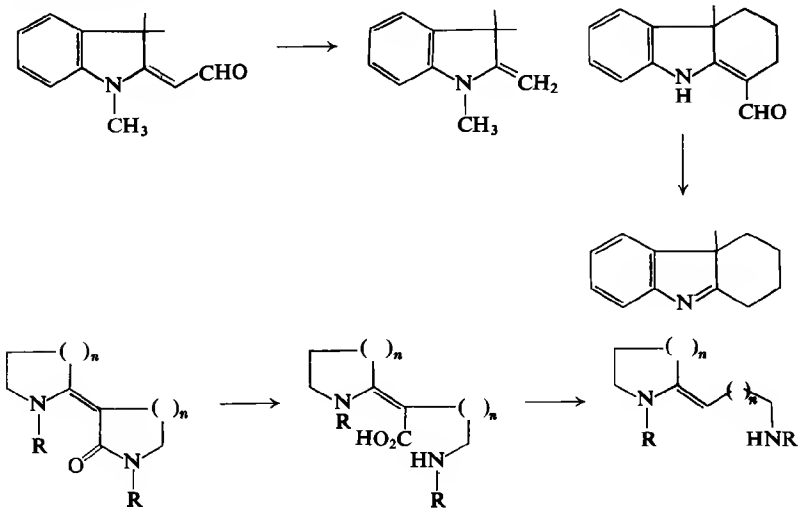
Analogously, enamines substituted with nitrile (*47,48*), ester (*49,50*), sulfone (*51*), and nitro groups (*52*) were obtained.



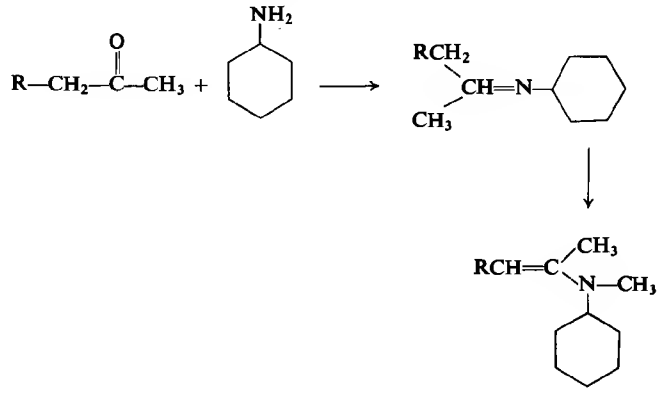
Vinylogous formamides have been obtained by double Vilsmeier reactions of methyl ketones (*53,54*), 4-methylpyridine (*53,54*), and olefinic (*55*) compounds. The dienamine intermediates were demonstrated in the latter cases.

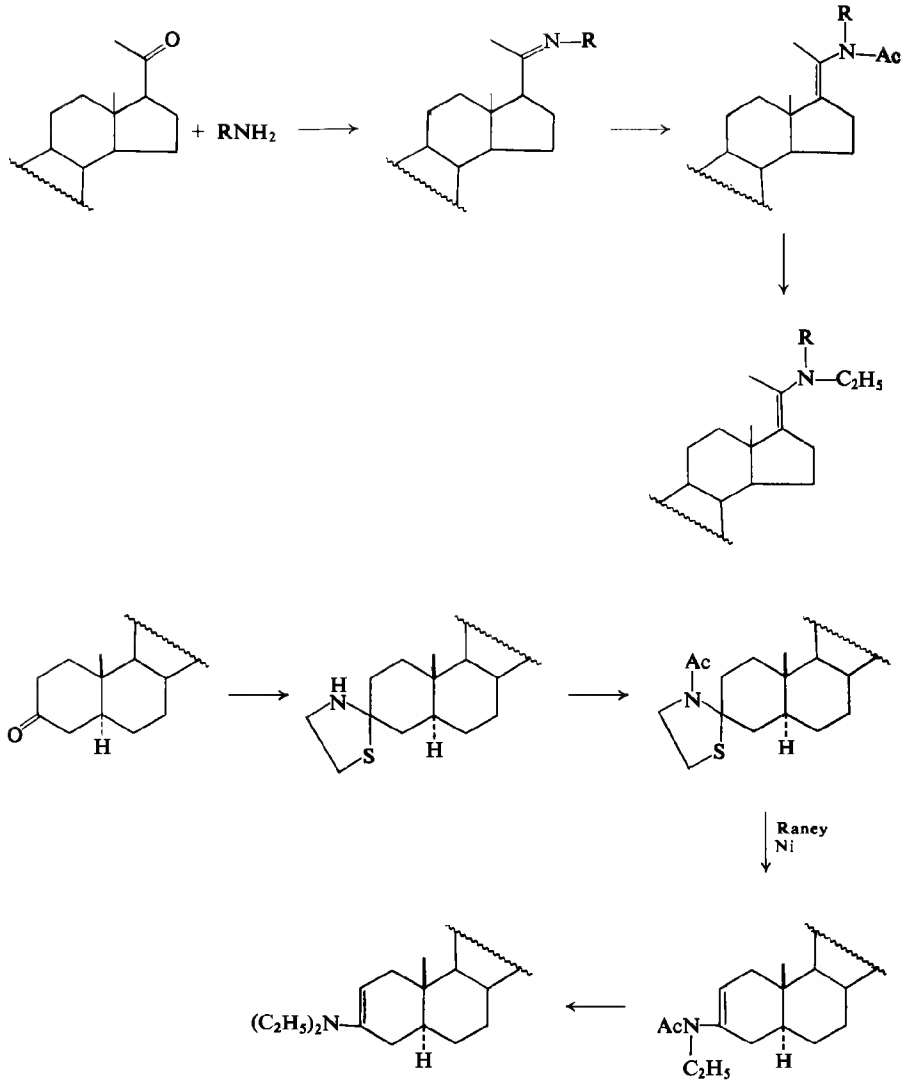


Hydrolytic cleavage of vinylogous formamides and ureas has been applied to the generation of enamines (*56–58*).



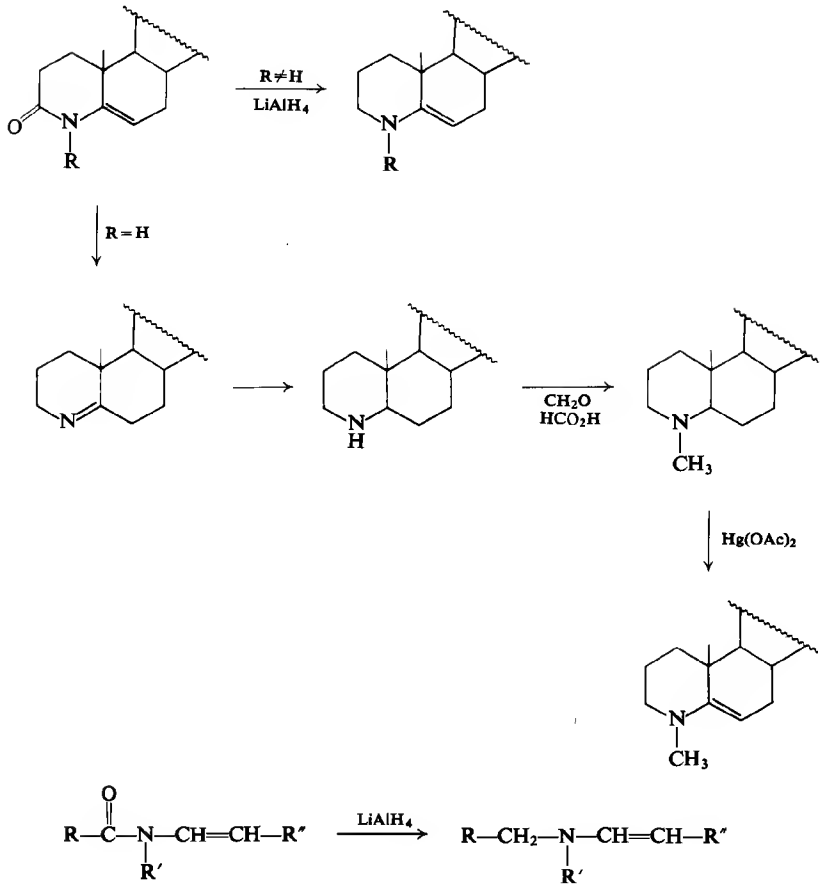
While enamines can usually be obtained directly from ketones and secondary amines their formation by an indirect route may be advantageous. The previously mentioned condensation of methyl ketones during azeotropic enamine formation has prompted the alklyation (*3*) or acylation and reduction (*59*) of Schiff's bases. A parallel method uses the formation and desulfurization of N-acylthiazolines followed by hydride reduction (*60,61*).



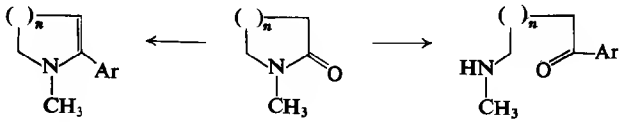


B. Formation of Cyclic Enamines

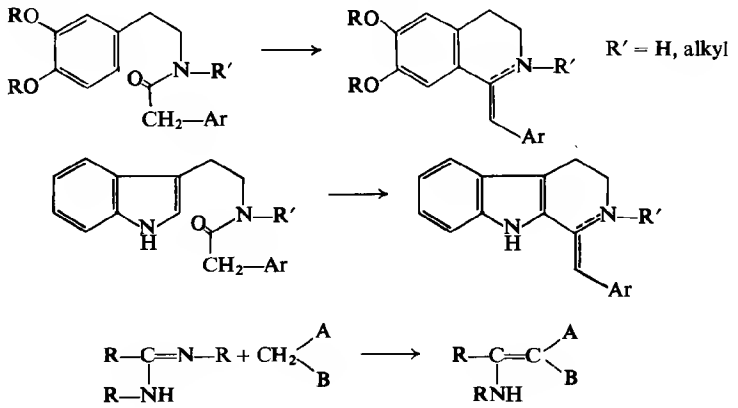
The reduction of enamides (*62–73*) has been applied primarily to the synthesis of cyclic enamines (*74–76*), but also to acyclic enamines (*77*).



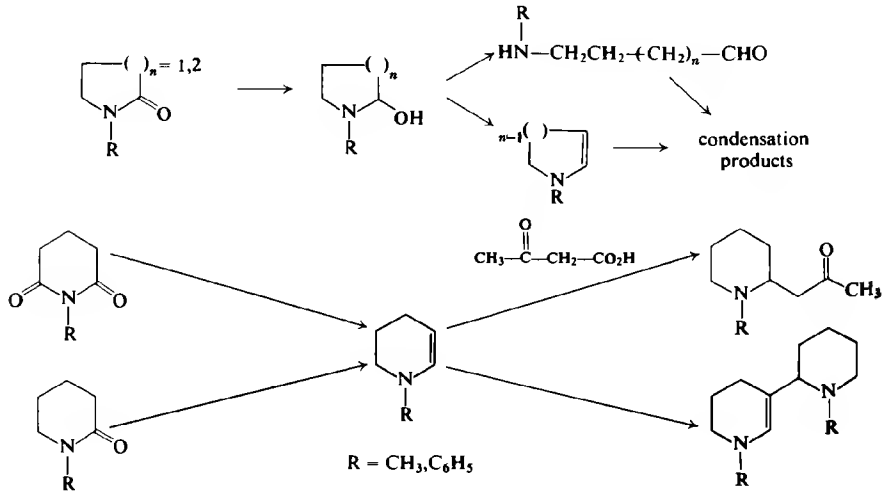
Cyclic enamines with an isomeric position of the double bond have been obtained by the addition of Grignard reagents to five- (*78–81*), six- (*82–86*), seven- (*87–90*), and thirteen- (*89–91*) membered lactams, whereas other medium-sized (*92,93*) lactams furnished amino ketones. The reaction has been extended to substituted lactams (*94–98*), and iminoethers (*99,100*).



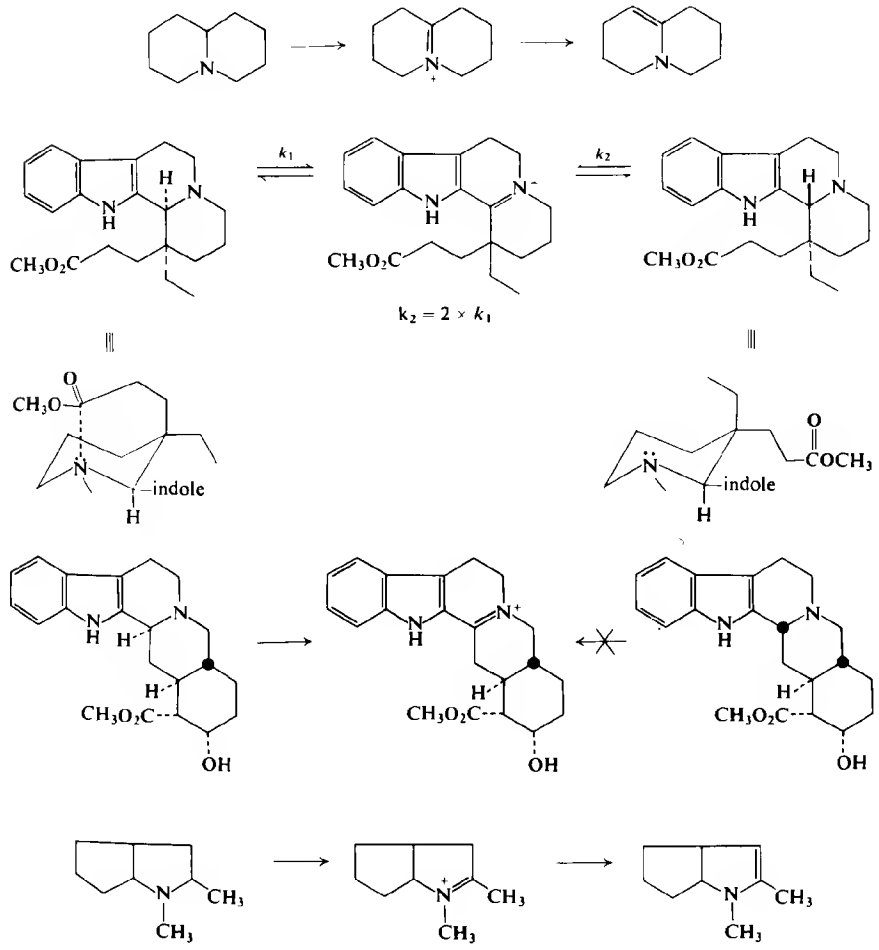
Formally analogous to the foregoing Grignard additions are the intramolecular condensations of amides with aromatic systems, found in the Bischler–Napieralski reaction (*101*), which is of particular interest in isoquinoline and indole alkaloid syntheses (*102*). Condensations of amidines with reactive methylene compounds also led to enamines (*103–106*).



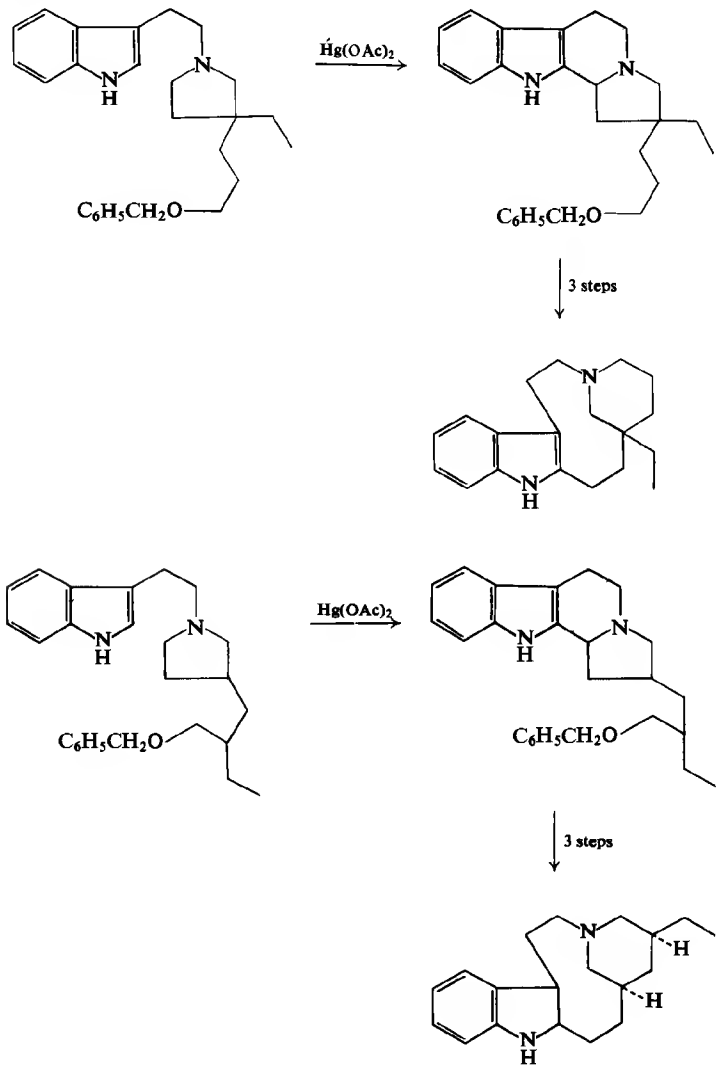
Partial reductions of N-alkylated lactams with lithium aluminum hydride (*107*) or sodium and butanol (*108,109*) and electrolytic reductions of N-methylglutarimide (*110*) have been reported.



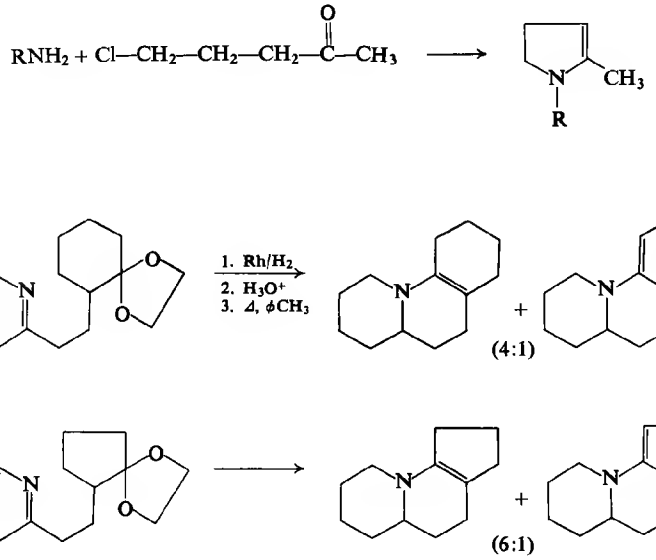
The most general method for synthesis of cyclic enamines is the oxidation of tertiary amines with mercuric acetate, which has been investigated primarily by Leonard (*111–116*) and applied in numerous examples of structural investigation and in syntheses of alkaloids (*102,117–121*). The requirement of a *trans*-coplanar arrangement of an α proton and mercury complexed on nitrogen, in the optimum transition state, confers valuable selectivity to the reaction. It may thus be used as a kinetic probe for stereochemistry as well as for the formation of specific enamine isomers.



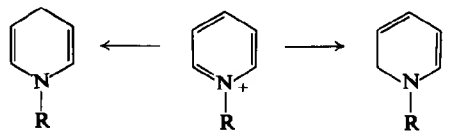
The key step in syntheses of *dl*-quebrachamine (*122–127*) and *dl*-dihydrocleavamine (*128*) is the oxidation of tertiary amines with mercuric acetate to cyclic imonium salts, which give rise to an intramolecular electrophilic attack on an indole.



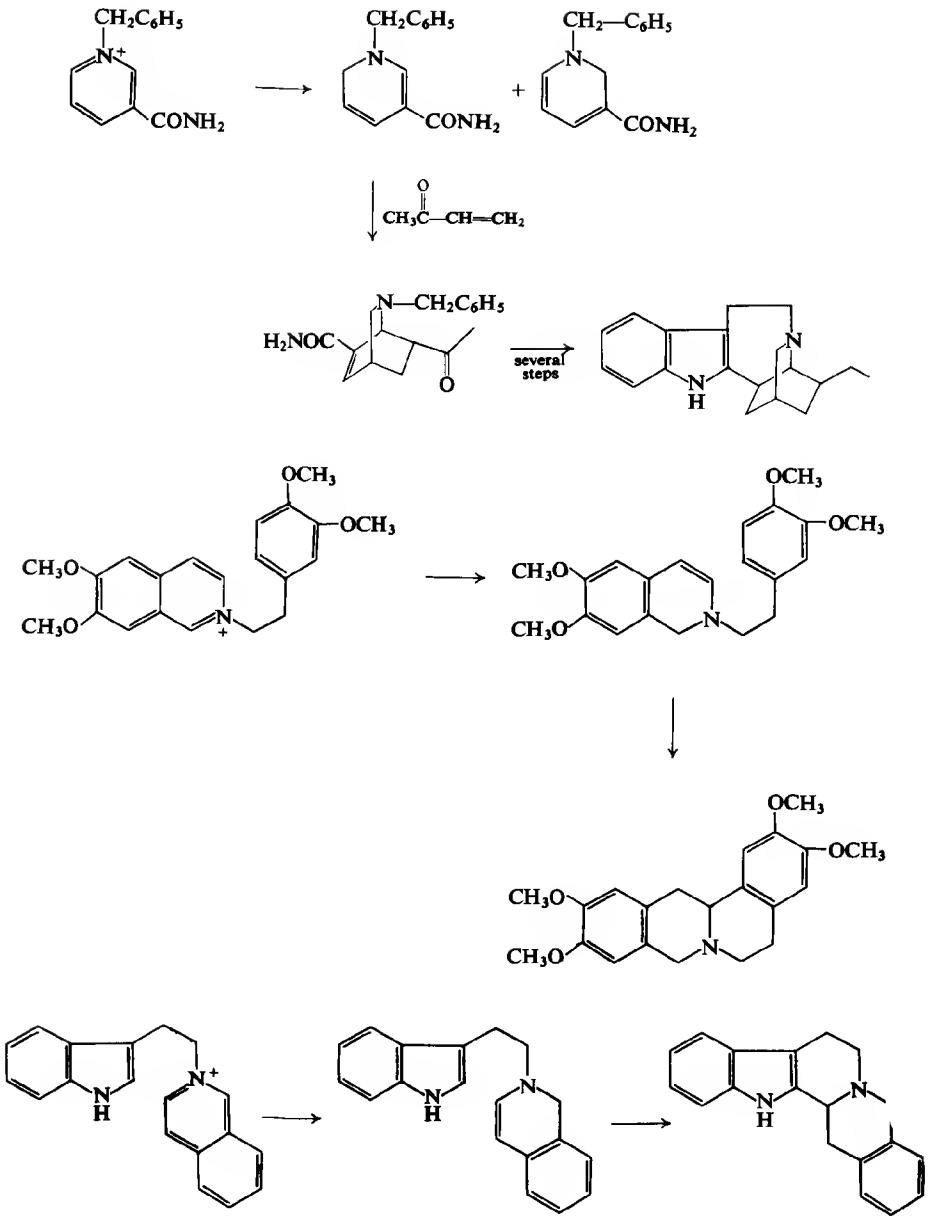
The synthesis of cyclic enamines through intramolecular reactions offers further structural flexibility (*129–135*).



The reduction (*136*) of pyridinium compounds to 1,2- or 1,4-dihydro products with complex metal hydrides or dithionite leads to cyclic dienamines of synthetic and biochemical interest.

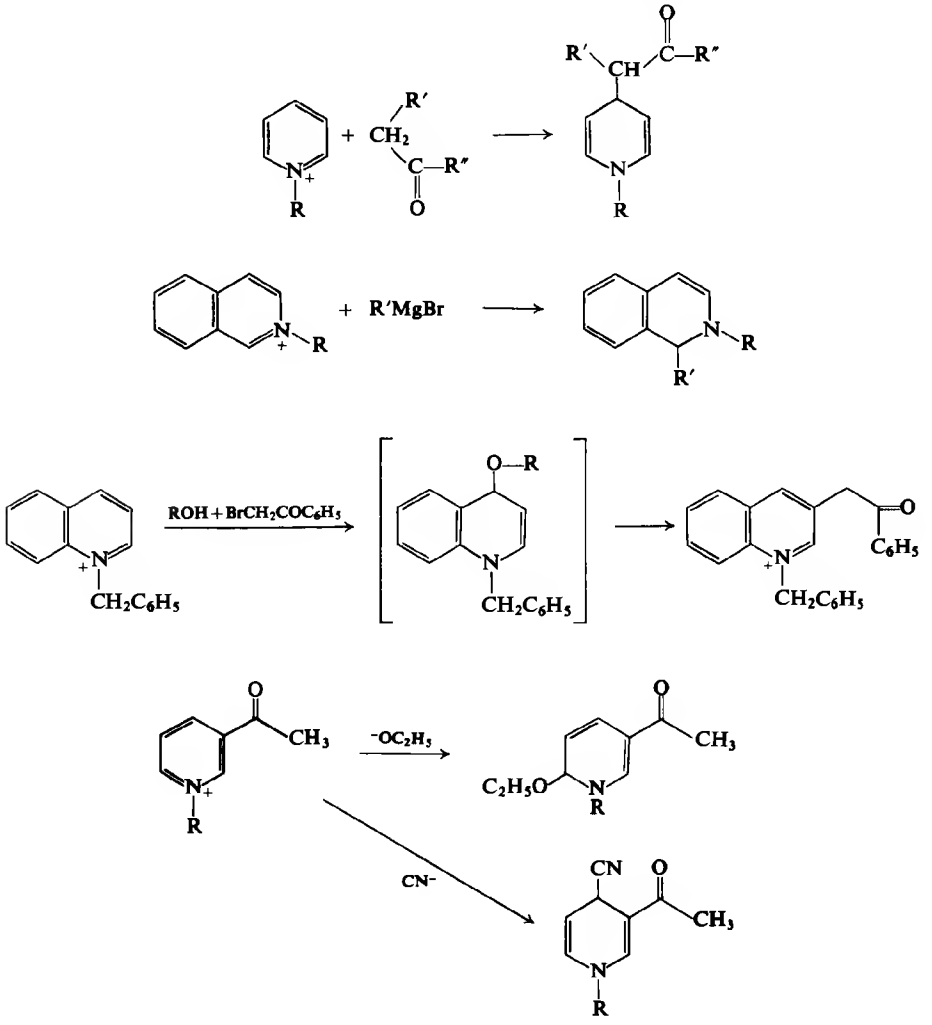


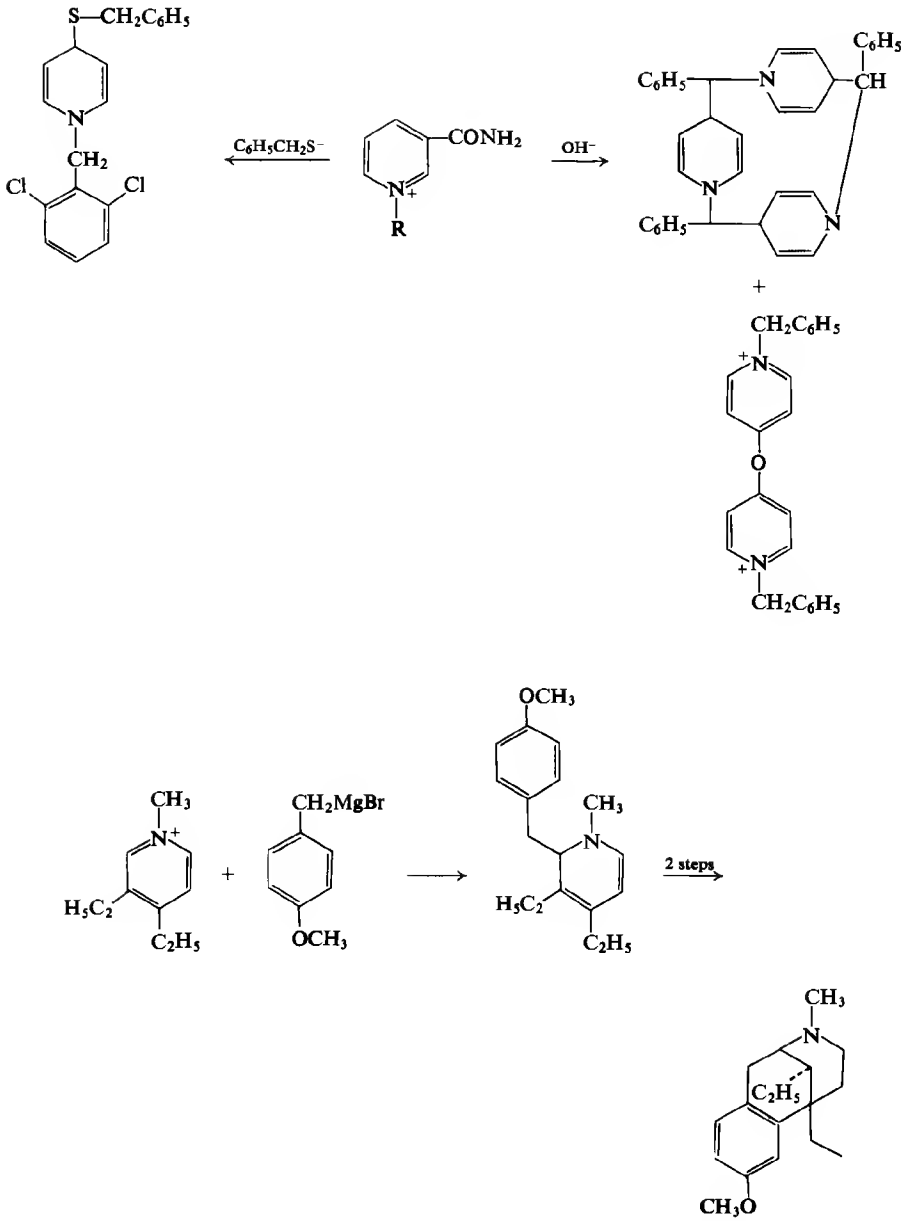
Thus the critical synthetic 1,6-dihydropyridine precursor for the unique isoquinuclidine system of the iboga alkaloids, was generated by reduction of a pyridinium salt with sodium borohydride in base (*137–140*). Lithium aluminum hydride reduction of phenylisoquinolinium and indole-3-ethylisoquinolinium salts gave enamines, which could be cyclized to the skeletons found in norcoralydine (*141*) and the yohimbane-type alkaloids (*142,143*).



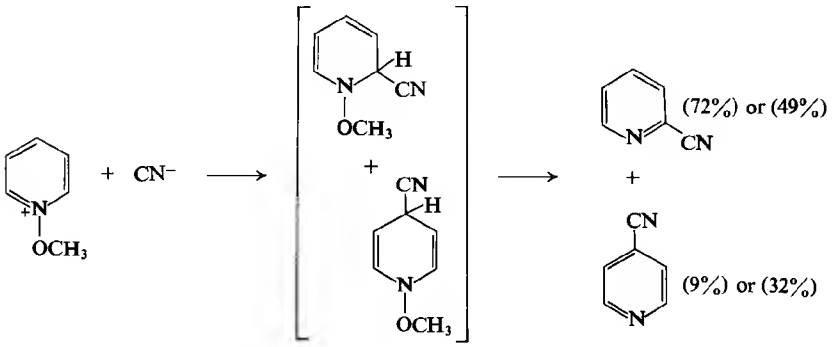
Analogous to DPNH (*144–146*), 1,4-dihydropyridines (*147*) act as reducing agents. For instance, the conversion of aromatic nitro compounds to amines (*148*) and reduction of enones to ketones (*149*) has been achieved.

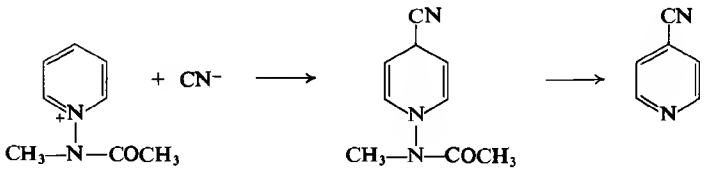
The addition (*150–157*) of Grignard reagents, alkoxides, hydroxide, sulfides, cyanide, and enolate anions to pyridinium and isoquinolinium salts again provides a variety of cyclic enamines of potential synthetic use.



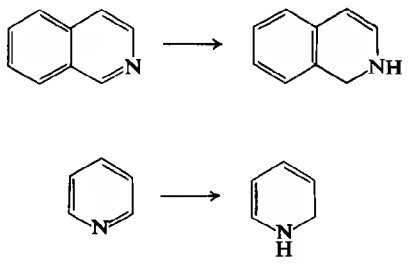


The reactions of pyridinium N-alkoxides (*158–161*) or pyridinium N-amides (*162*) with cyanide demonstrate a useful substitution reaction for pyridines.

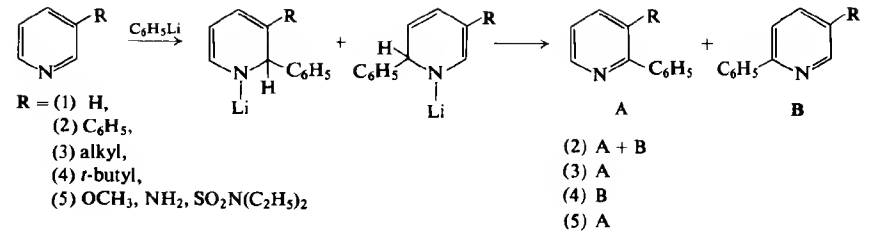


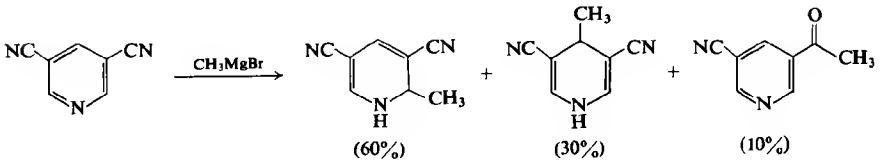


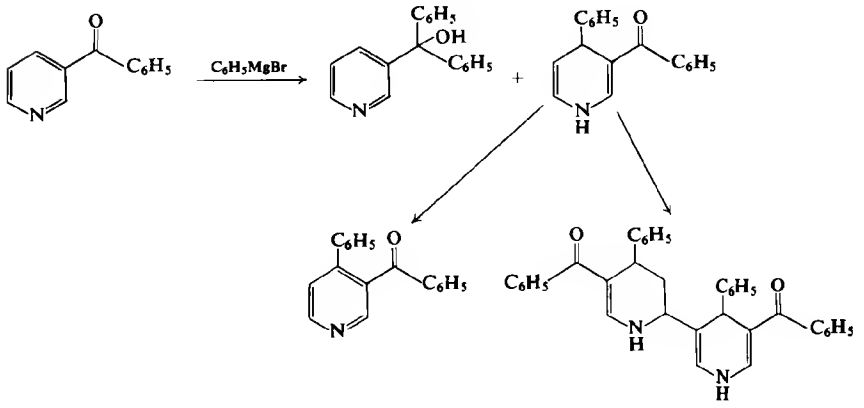
Cyclic enamines can also be obtained by the reduction of pyridine and isoquinoline with lithium aluminum hydride (*163–165*), and the latter reduction has also been accomplished with sodium in liquid ammonia (*166*).



Similarly, the addition of organometallic reagents to pyridines leads to dienamine intermediates, which can be demonstrated (*167–170*).

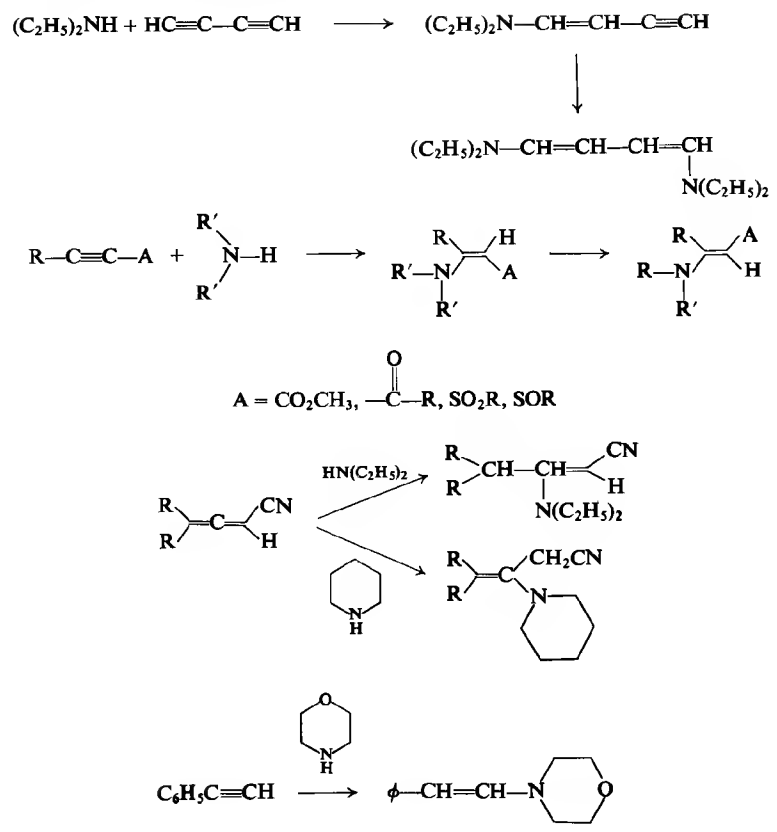




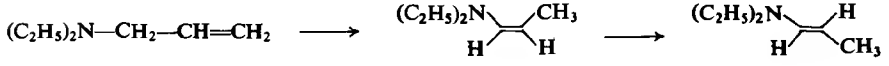


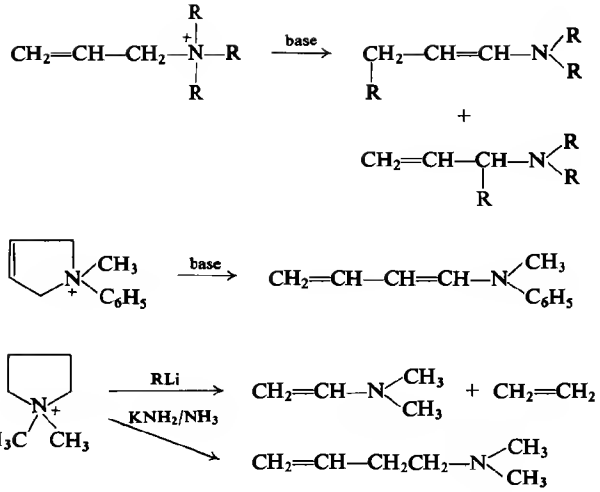
C. Other Methods of Enamine Formation

The addition of secondary amines to acetylenes is most applicable to the synthesis of conjugated acyclic enamines (*50,171,172*). Particularly the addition to acetylenic esters and sulfones has been investigated (*173–177*) and it appears that an initial *trans* addition is followed by isomerization to more stable products where the amine and functional group are in a trans orientation (*178*). Enamines have also been obtained by addition of secondary amines to allenes (*179*).

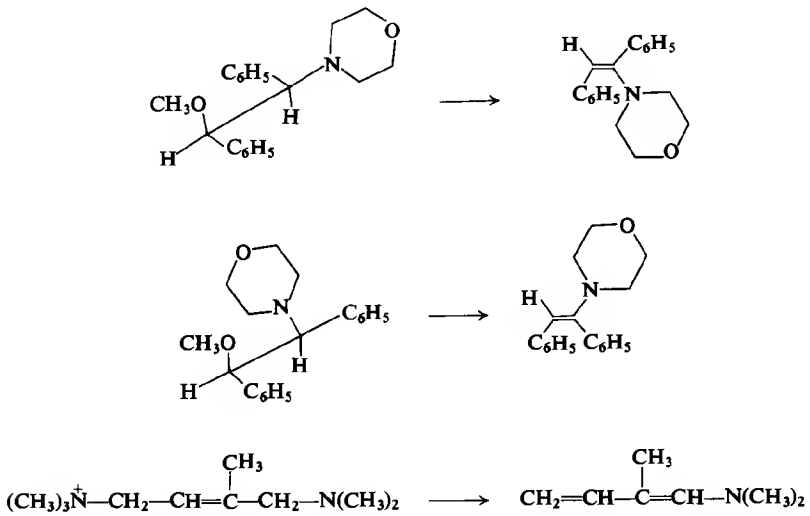


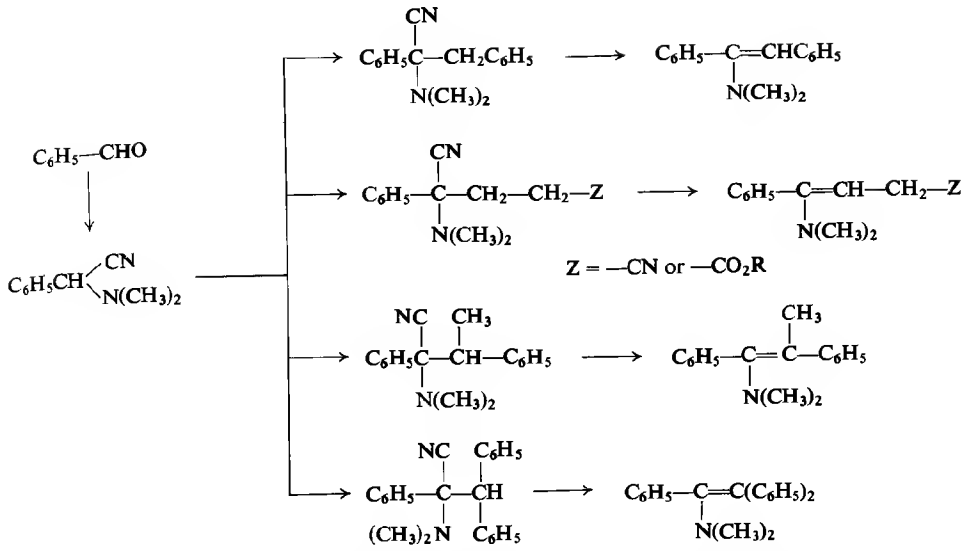
Of further interest is the base catalyzed isomerization of allylic amines to enamines, in which the *cis*-substituted olefin appears again as the initial kinetic product and subsequently isomerizes to the more stable *trans*-substituted product (*180,181*). The closely related rearrangement of allylic ylids leads to enamines as well as allylic amines (*182,183*). Especially striking are the generation of a dienamine by ring opening of a 3,4-didehydropyrrolidinium salt (*184*) and the fragmentation of a corresponding saturated ylid to yield ethylene and an enamine (*185,186*).



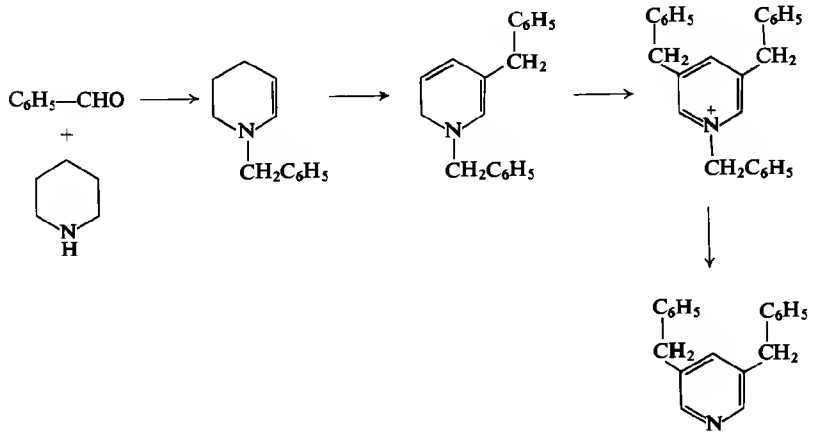


The stereospecific generation of enamines by β-elimination reactions (*187*) and a vinylogous β elimination, which leads to a dienamine (*188*), have been reported. The loss of an α substituent from a tertiary amine is seen in the generation of enamines by elimination of hydrogen cyanide from benzylic α-aminonitriles (*189,190*).



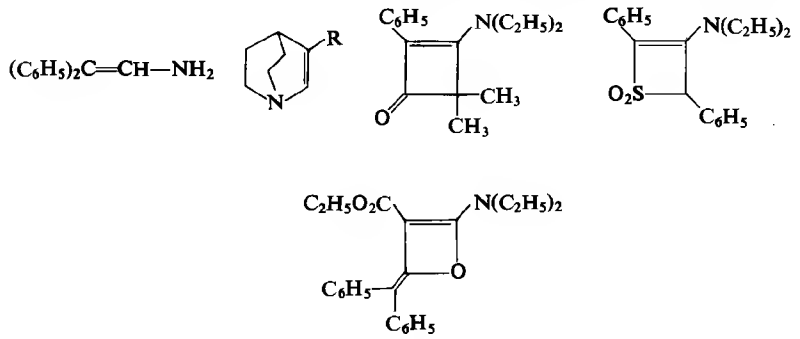


In the generation of 3,5-dibenzylpyridine from piperidine and benzaldehyde, the formation of enamine and dienamine intermediates must also be involved (*191–193*).



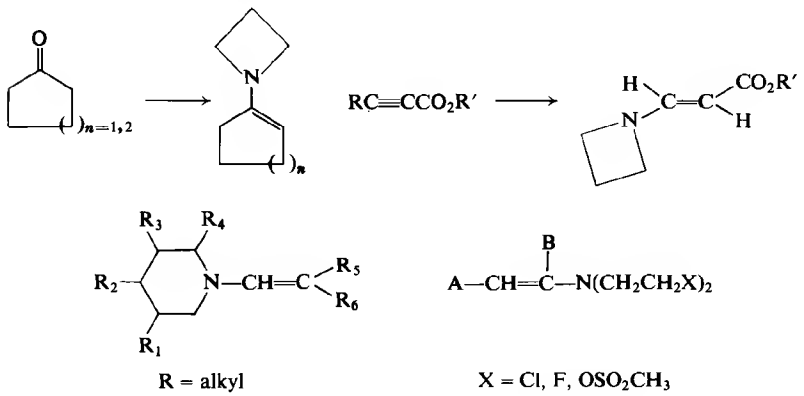
Some enamines with special structural features are those derived from ammonia (*194*) and the quinuclidine enamines (*195*). Aminocyclobutenes

and four-membered heterocyclic enamine compounds are also known and particularly available through addition reactions of ynamines (*196–198*).



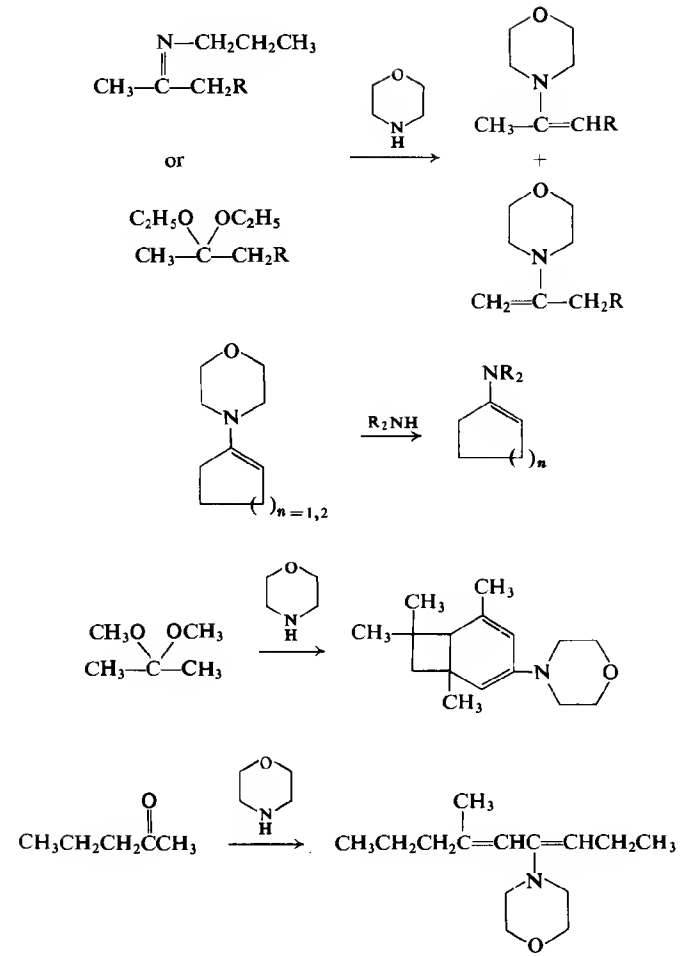
D. Additional Examples of Enamine Formation

Recent enamine preparations have included azirene (*633*) and substituted piperidine (*634*) derivatives. Enamines with bis-β-haloalkylamine substituents were found to be antitumor agents with a biological activity that did not exceed the activity of the parent secondary amine (*635*). The formation of enamines by exchange reactions of Schiff's bases, ketals, and morpholine enamines (*636*) has been studied further and could be used for some methyl-ketone-derived enamines. However, the dimethylketal of acetone yielded a tetrameric condensation product (*637,638*). The tendency of methyl ketones to undergo condensation during enamine formation was applied in a preparative route to cross-conjugated dienamines (*639*).

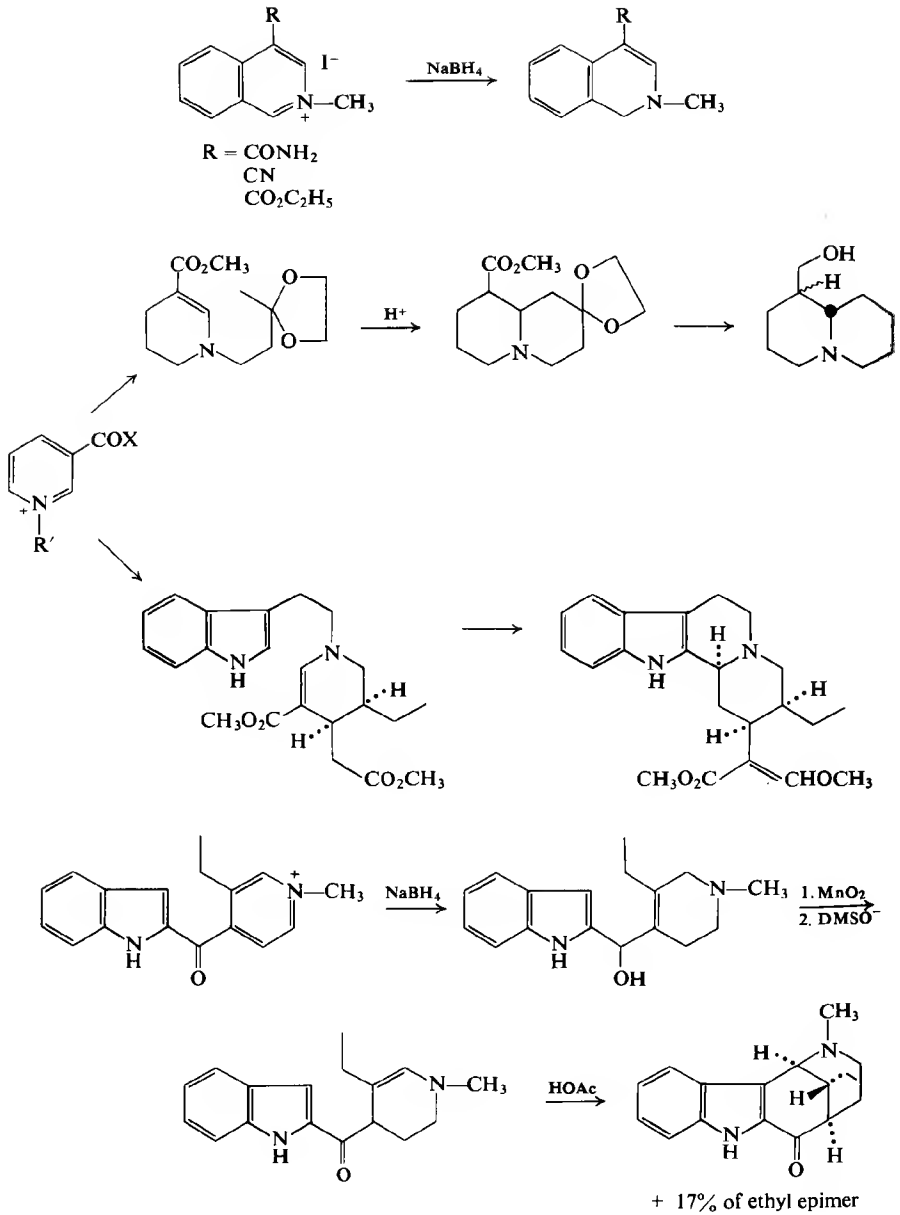


R = alkyl

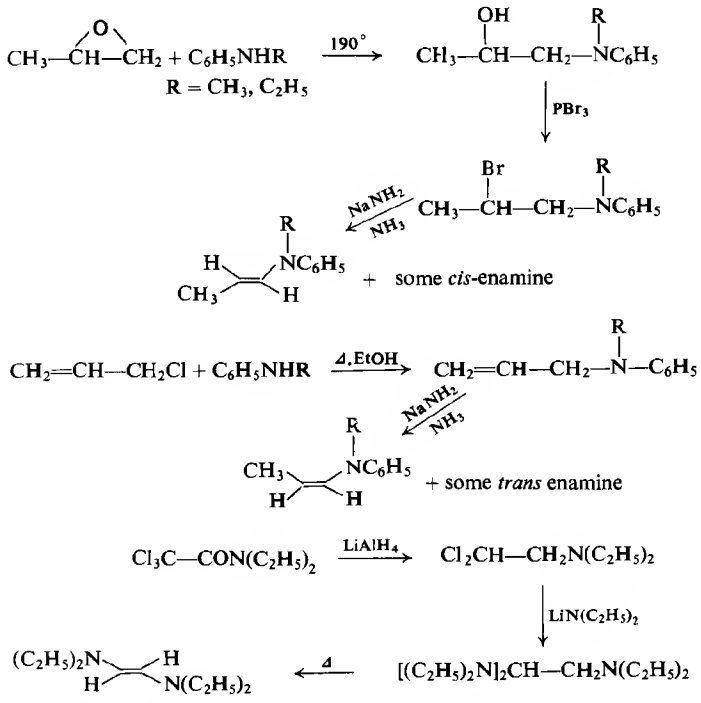
X = Cl, F, OSO_2CH_3



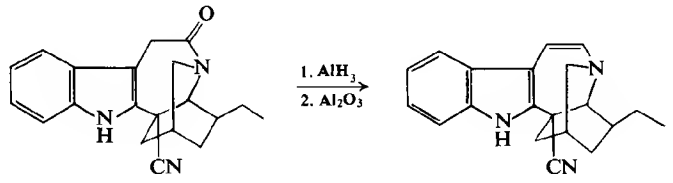
Sodium borohydride reduction of 4-substituted isoquinolinium salts led to vinylogous cyanamides, ureas, and urethanes, as well as the corresponding tetrahydroquinolines (*640*). Hydrogenation of β-acylpyridinium salts (*641*) to vinylogous ureas was exploited in syntheses of alkaloids (*642*), leading, for instance, to lupinine, epilupinine, and corynantheidine (*643, 644*). Similarly, syntheses of dasycarpidone and epidasycarpidone were achieved (*645*) through isomerization of an α,β-unsaturated 2-acylindole and cyclization of the resultant enamine.

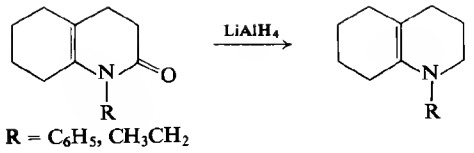


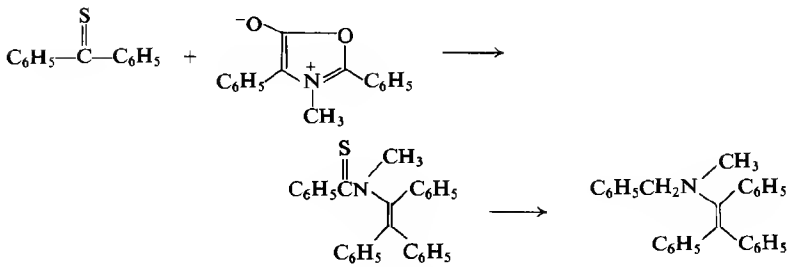
Aromatic enamines were prepared by dehydrohalogenation of β-bromoamines with strong base. While *trans* enamines were thus formed, one obtained mostly *cis* enamines from rearrangement of the corresponding allylic amines under similar reaction conditions (*646*). Vicinal endiamines were obtained from β-dichloroamines and lithium amides (*647*).



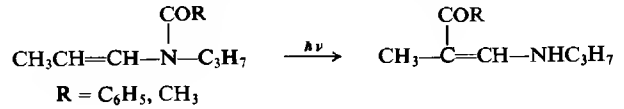
An enamine was obtained in the synthesis of coronaridine (*648*) by aluminum hydride reduction of a bridged lactam, followed by dehydration on alumina. Additional examples of enamine formation by reduction of enamides (*649*) and thioenamides (*650*) were reported.

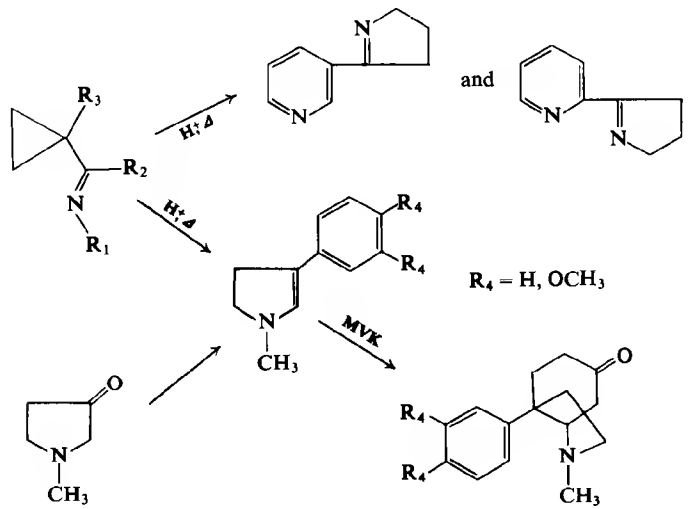




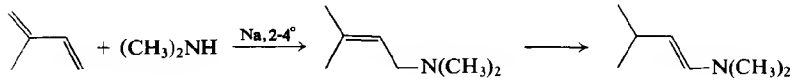


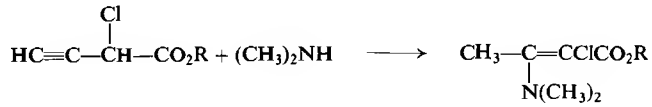
The photochemical rearrangement of enamides to vinylogous amides was described (*651,652*). Rearrangement of cyclopropyl ketimines to enamines with acid was applied to syntheses of myosamine, apoferrosamine, mesembrine, and desmethoxymesembrine (*653–656*).

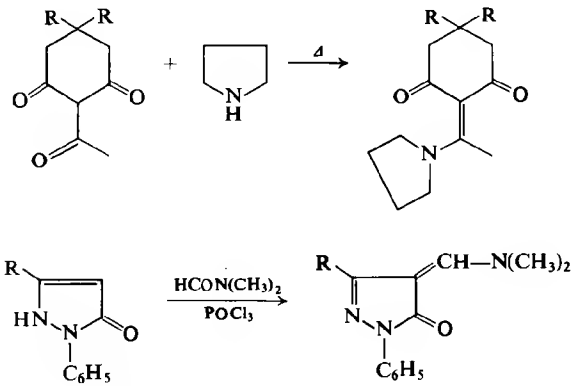


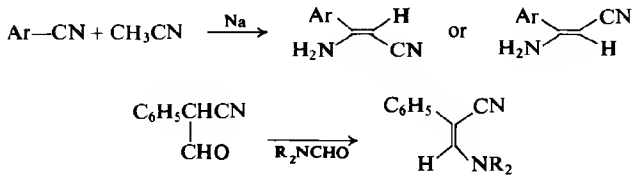


The addition of secondary amines to conjugated dienes and isomerization of the allylic amine products (*657*) provided an attractive expansion of enamine chemistry. A chlorinated vinylogous urethane was formed by amine addition to an acetylene and double-bond rearrangement (*658*). Further examples of enamines conjugated with electron-withdrawing groups were provided by previously indicated synthetic methods (*659–661*). The use of a formamide in conversion of an α-cyano aldehyde to a vinylogous cyanamide avoided the deformylation experienced with the corresponding secondary amine (*662*).



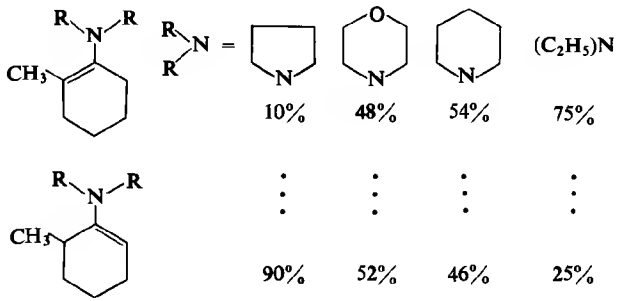


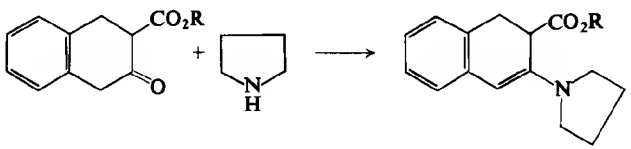


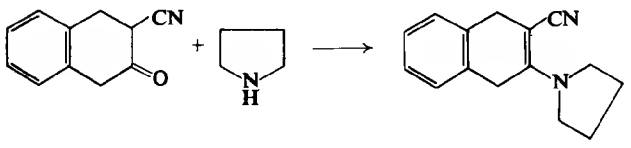


III. Structure of Enamines

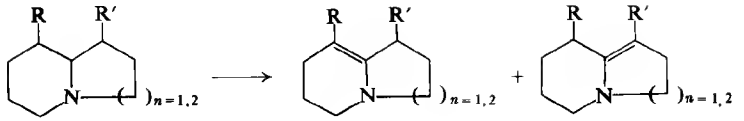
To the synthetic chemist, enamines will only be useful in substitution reactions if their structures are unambiguous. When isomeric positions are available, the location of the double bond is not always obvious. It could be shown, for instance, that the double-bond position of 2-methylcyclohexanone enamines (*199,200*) depends on the degree of overlap of the nonbonding electrons on nitrogen with the double bond and thus on the structure of the amine. A remarkable contrast was found in the pyrrolidine enamines of 3-carbethoxy and 3-cyano-2-tetralones, where the double bond was generated in conjugation with the benzene ring and the cyano group, respectively (*201*).







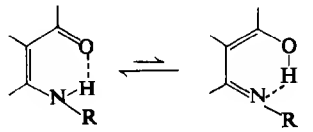
The oxidation of unsymmetrical tertiary amines with mercuric acetate may also lead to isomeric enamines. In such cases, structures can often be established by NMR and IR spectra of the enamines and their corresponding imonium salts, through comparison with model systems (*202–205*).

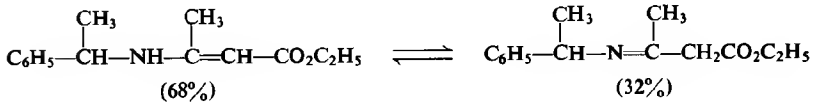


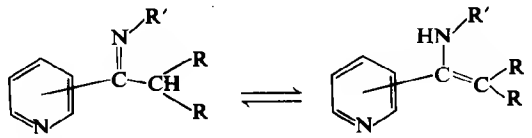
R = H, CH_3

R′ = H, CH_3, C_2H_5, C_6H_5

Spectroscopic investigation of enamines conjugated with ketone, ester and nitrile groups established the prevalence of enamine rather than imine–enol tautomers in examples of secondary amines (*206–212*). Similar studies have been made with enamines of acylpyridines and acetophenones (*213,214*).



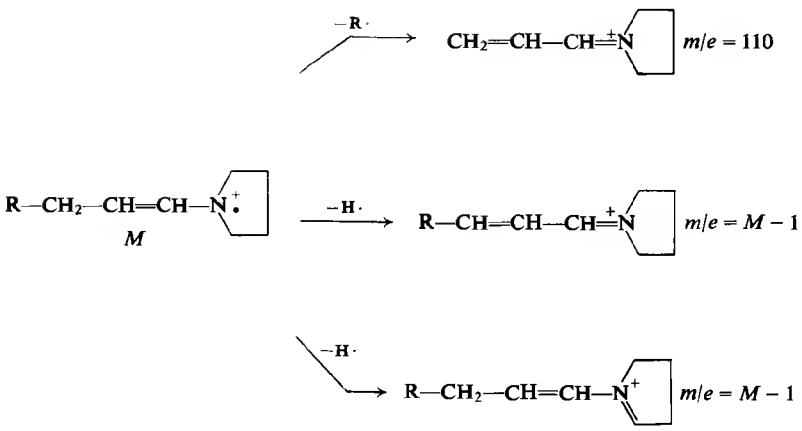




proportion of enamine:

2-pyridyl > 4-pyridyl > 3-pyridyl > C_6H_5

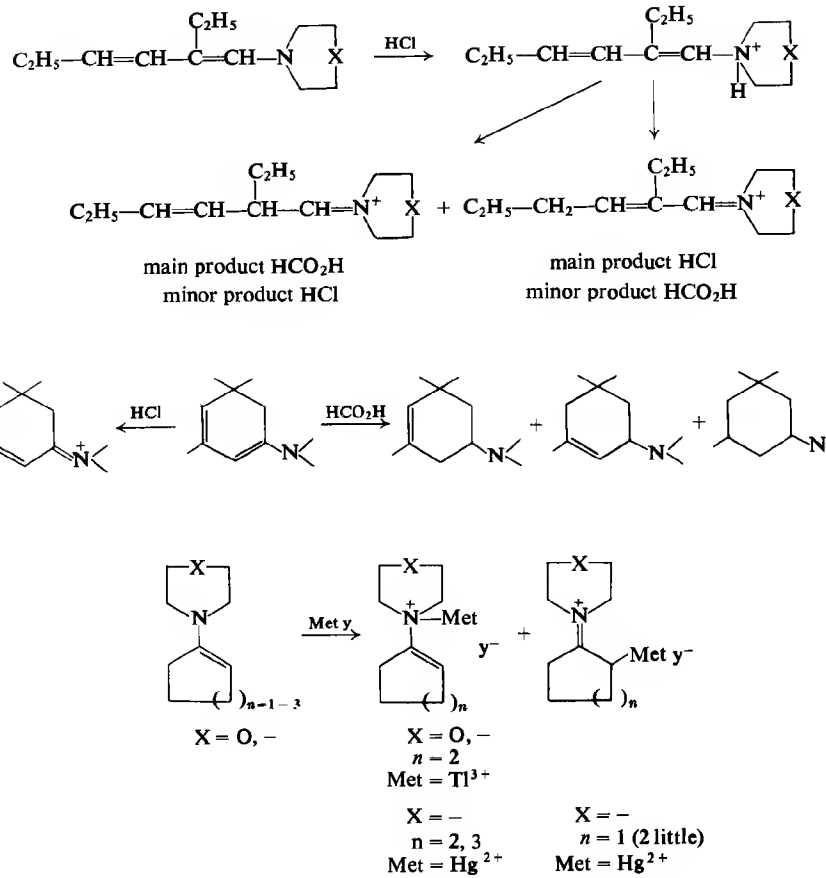
The mass spectra of enamines (*215,216*), and optical rotatory dispersions (*217*) of optically active enamines have also been used for structural assignments.



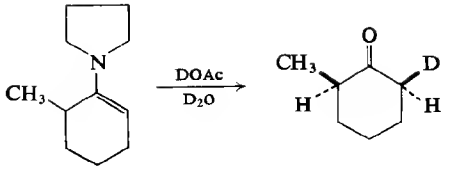
Ultraviolet absorptions of vinylogous lactams were found by MOLCAO calculations and compared with experimental values (*663*). Infrared spectroscopic studies of vinylogous amides (*664*) and some fifty vinylogous urethanes (*665*) allowed configurational and structural assignments. The effect of enamine–imine equilibrium in a series of benzophenone derivatives was established (*666*) and the effect of structure on enamine basicity studied (*667*).

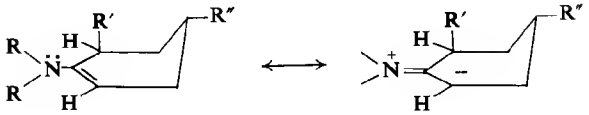
IV. Protonation of Enamines

Some of the important factors affecting the reactions of enamines with other electrophiles are seen in their reactions with acids. While the formation of imonium salts has long been recognized (*10,34,218–223*), and correlated with an infrared shift of the double bond to higher frequencies, subsequent studies have shown that amonium salts may be formed as kinetic products, which then rearrange to more stable imonium salts (*224–226*). The ease of protonation on carbon depends upon the structures of the amine and olefinic moieties of the enamine. Relative basicities of enamines and their rates of hydrolysis have been studied (*227,228*). With dienamines, rearrangement of the amonium to the imonium salt is influenced by the nature of the acid (*20,229–231*). In the reactions with mercuric (*232,233*), tin (*229*), and thallic (*21*) salts, metalation may take place on carbon or on nitrogen, depending on the nature of the enamine and the cation.

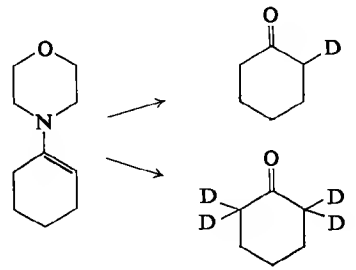


The reactions of pyrrolidinocyclohexenes with acid have also been considered from a stereochemical point of view. Deuteration of the 2-methylcyclohexanone enamine gave *cis*-2-deuterio-6-methylcyclohexanone under conditions where *cis*-4-*t*-butyl-6-methylpyrrolidinocyclohexene was not deuterated (*234*). This experiment supported the postulate of Williamson (*235*), which called for the axial attack of an electrophile and axial orientation of the 6 substituent on an aminocyclohexene in the transition state of such enamine reactions. These geometric requirements explain the more difficult alkylation of a cyclohexanone enamine on carbon 2, when it is substituted at the 6 position, as compared with the unsubstituted case.





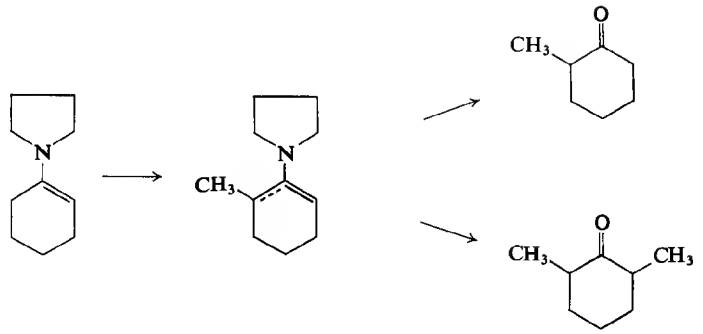
Enamines have also found use in the preparation of α-deuterated ketones (*236*).



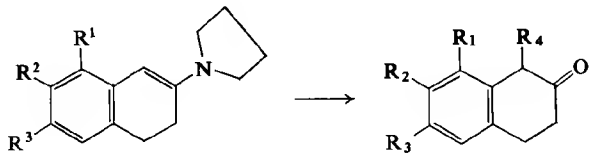
V. Alkylation of Enamines

A. With Alkyl Halides

The illumination of enamines as general activating derivatives of ketones in alkylation reactions also threw light on their special usefulness for controlling alkylations (*3*), particularly in the formation of monosubstituted cyclohexanones. Thus 2-methylcyclohexanone could be obtained in 80% yield from the pyrrolidine enamine of cyclohexanone, and further alkylation, which required more drastic conditions, gave only 2,6-dimethylcyclohexanone (*1,237*).

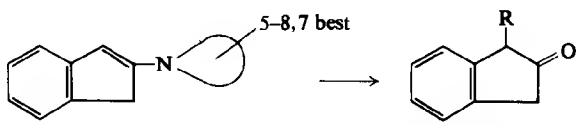


In the alkylation of enolate anions, a mixture of mono- and polyalkylation products is usually obtained, and when enolization of a di-α-methylene ketone is possible toward both sides, a mixture of di-α- and α,α′-dialkylation products can be expected. Thus the enamine alkylation sequence becomes particularly attractive when controlled monoalkylation is imperative because of difficulties in separation of a mixture of alkylation products. One of its first synthetic applications was in the reactions of β-tetralones with alkyl halides. Yields in excess of 80% were usually found (*238–243*) in these reactions, which make valuable intermediates for steroid and diterpene syntheses more accessible.

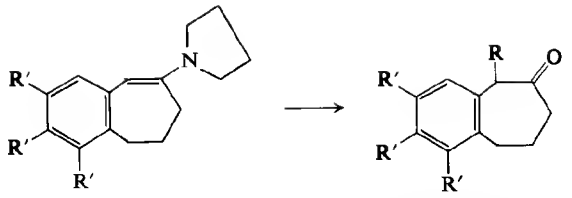


R_1, R_2, R_3 = H, OCH_3, isopropyl
$R_4 = CH_3, CH_2CO_2C_2H_5$

Similarly, the method has been applied to the synthesis of five- (*244*) and seven- (*245,246*) membered-ring ketone analogs of β-tetralone.



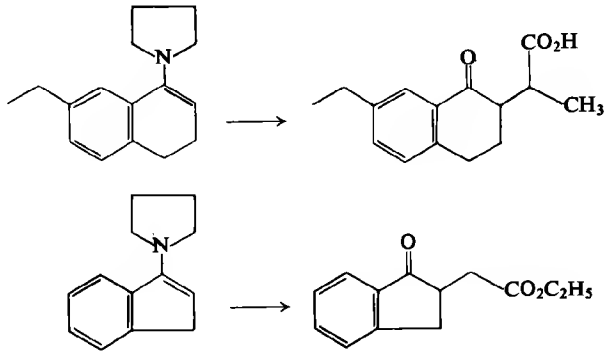
R = CH_3, $CH_2C_6H_5$, $CH_2OCH_2C_6H_5$



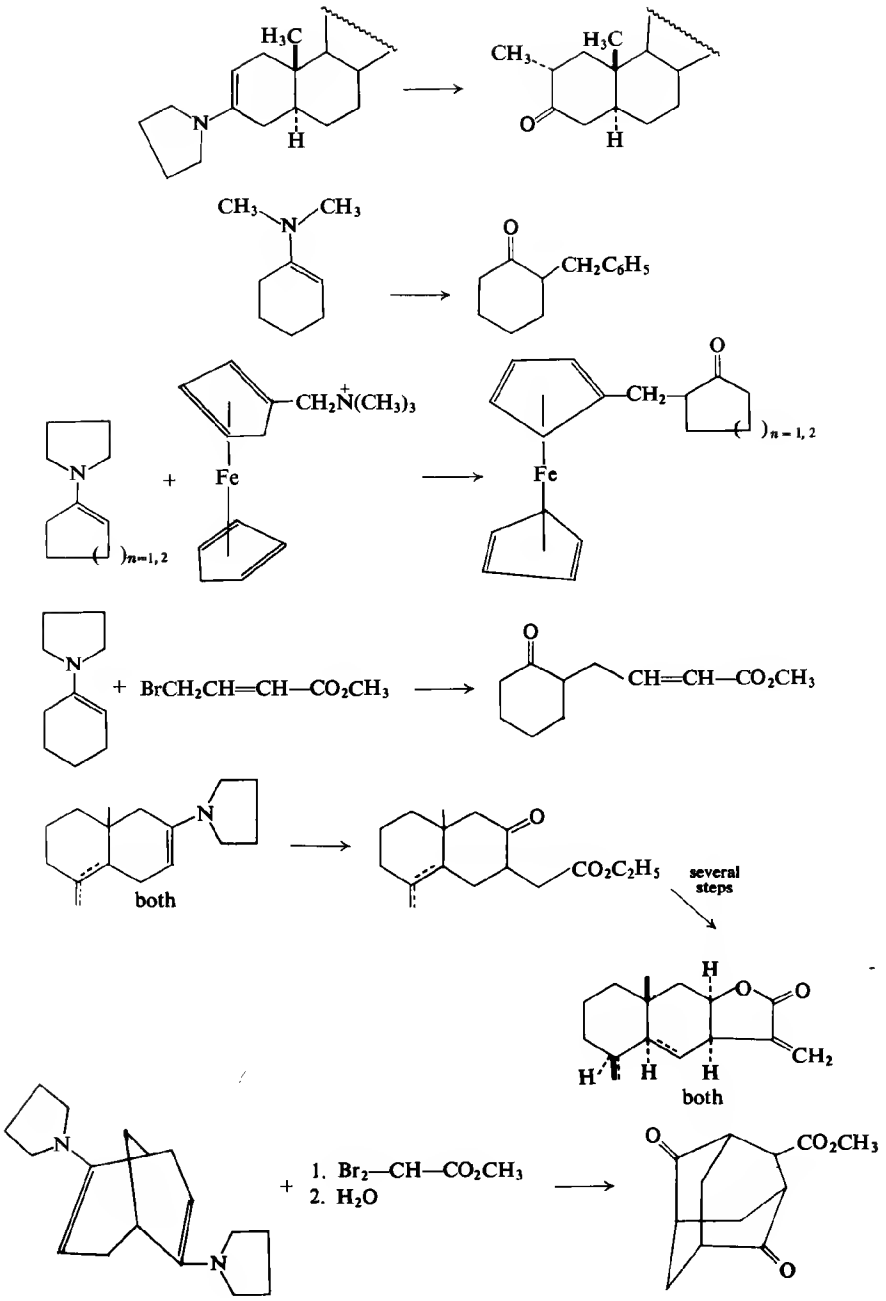
R = CH_3, $CH_2CO_2C_2H_5$, CH_2CH_2CN, $CH_2CH_2CO_2C_2H_5$

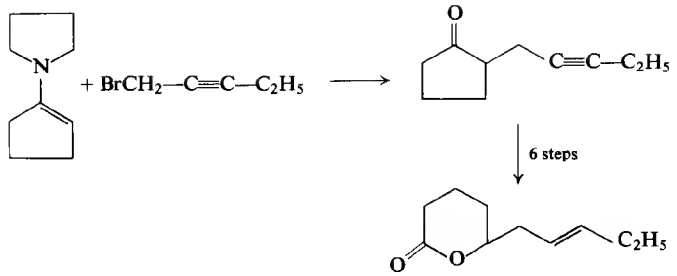
R′ = H, OCH_3

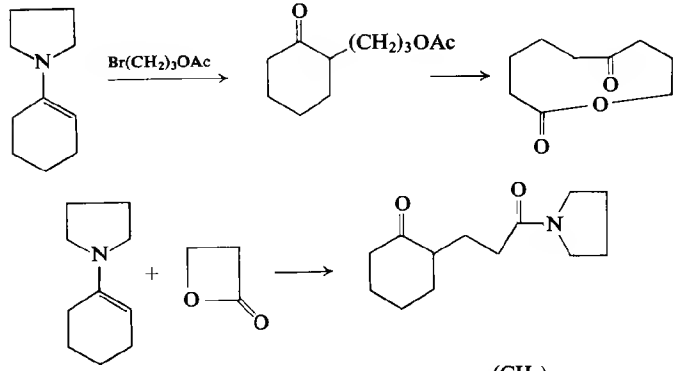
Extensions of the enamine alkylation to α-tetralones have also been used (*245–248*), but product yields were lower, presumably due to steric crowding in a transition state where generation of an imonium salt gives rise to a repulsion between a methylene group on nitrogen and a peri aromatic proton.

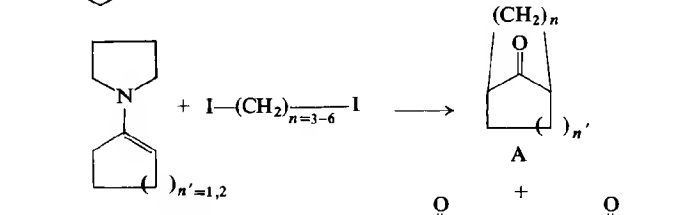


Other interesting synthetic applications of the ketone-derived enamine alkylation are found in the monomethylation of steroid enamines (*249*), extension of the benzylation reaction (*250*) to a ferrocene derivative (*251*), the use of α-bromoesters (*252*) and ketones (*252*) or their vinylogues (*253*), in the syntheses of alantolactone (*254–256*), isoalantolactone (*257*), and with a bridged bis-enamine (*258*). The use of bifunctional alkylating agents is also seen in the introduction of an acetylenic substituent in the synthesis of the characteristic fragrant constituent of jasmine (*259*), the synthesis of macrocyclic ketolactones (*260*), the use of butyrolactone (*261*), and the intermolecular or intramolecular double alkylations of enamines with dihalides (*262*).

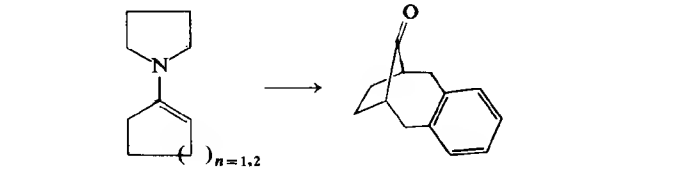




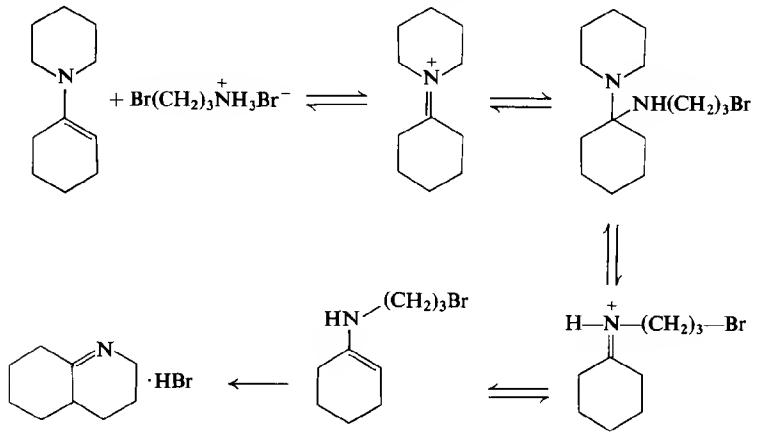




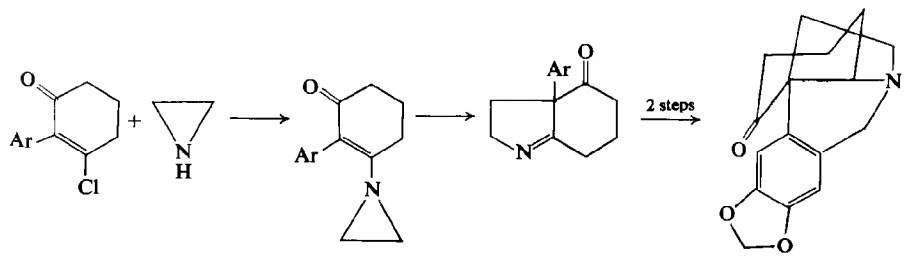
		A, %	B, %	C, %
$n' = 1$	$n = 3$	0	0	10
	$n = 4$	22	0	0
	$n = 5$	0	0	37
$n' = 2$	$n = 3$	0	0	7
	$n = 4$	15	9	0
	$n = 5$	0	25	21
	$n = 6$	0	20	2

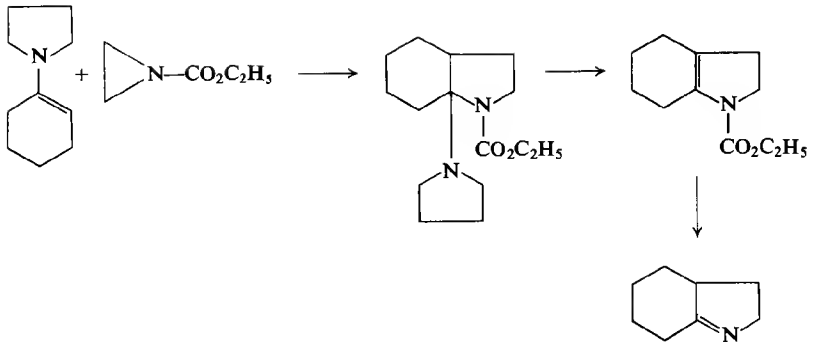


The formation of bicyclic imines (*263,264*) from piperidine enamines and γ-bromopropyl amines may appear at first sight to be a simple extension of the reactions of enamines with alkyl halides. However, evidence has been found that the products are formed by an initial enamine exchange, followed by an intramolecular enamine alkylation. Thus γ-bromodiethylaminopropane does not react with piperidinocyclohexene under conditions suitable for the corresponding primary amine. Furthermore, the enamine of cyclopentanone, but not that of cyclohexanone, requires a secondary rather than primary γ-bromopropylamine, presumably because of the less favorable imine to enamine conversion in this instance.

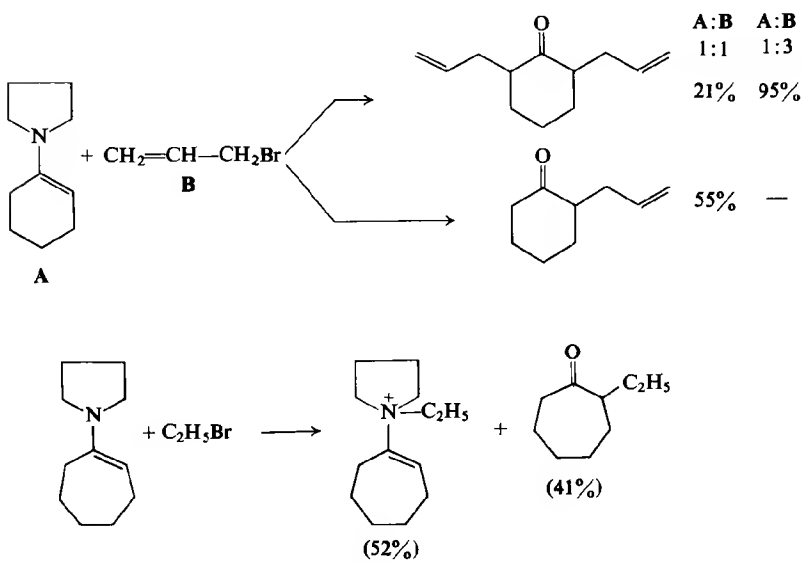


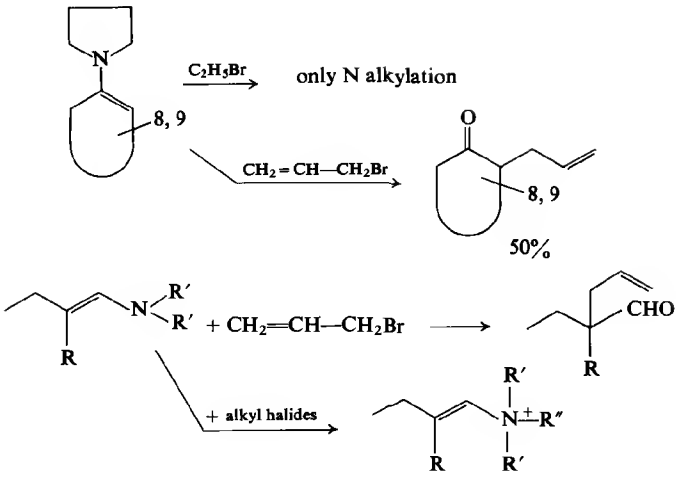
A related enamine alkylation is seen in the rearrangement of an ethylene imine vinylogous amide, which was heated with sodium iodide in diglyme. The presumed internal enamine alkylation constitutes a critical step in an oxocrinane synthesis (*265*). Use of an ethylene imine urethane for alkylation of an enamine and formation of the hexahydroindole system has also been reported (*266*).



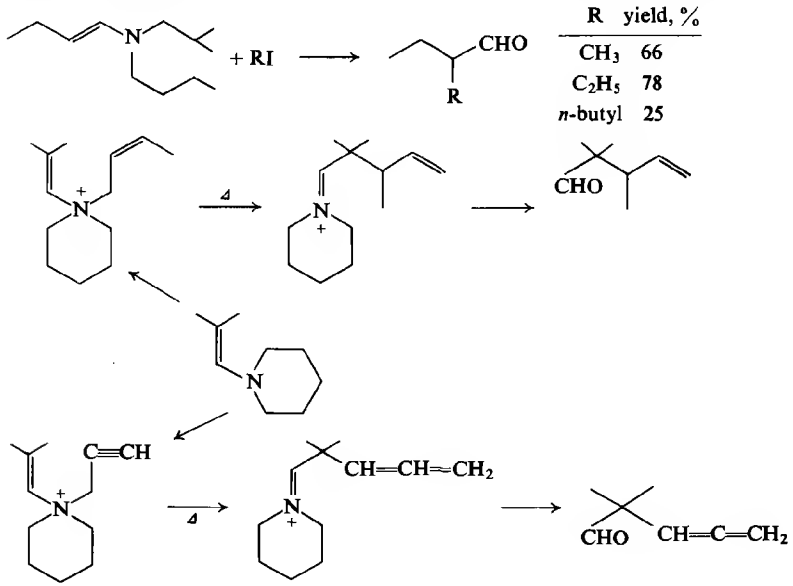


A fundamental problem in the alkylation of enamines, which is inherent in the bidentate system, is the competition between the desired carbon alkylation and attack at the nitrogen. With unactivated alkyl halides (*3,267*), this becomes especially serious with the enamines derived from cycloheptanone, cyclooctanone, cyclononanone, and enamines derived from aldehydes. Increasing amounts of carbon alkylation are found with the more reactive allyl and benzyl halides (*268–273*). However, with allyl halides one also observes increasing amounts of dialkylation of enamines.

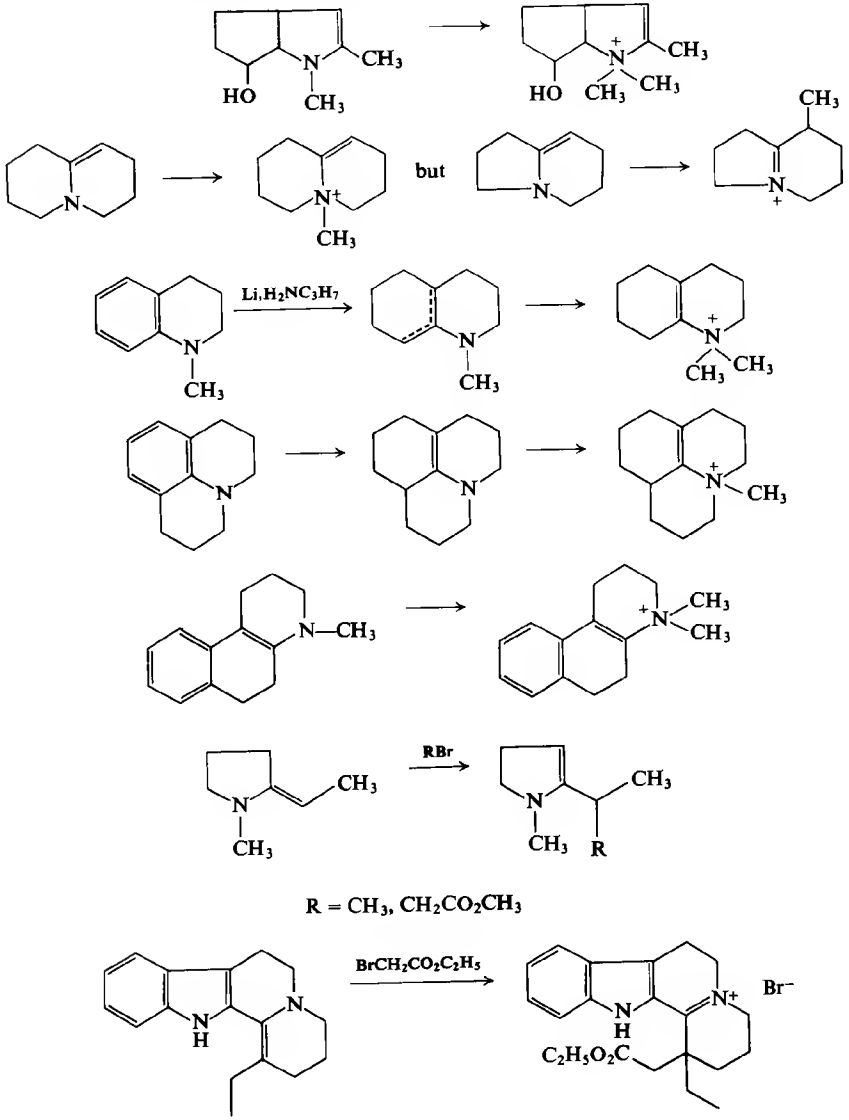




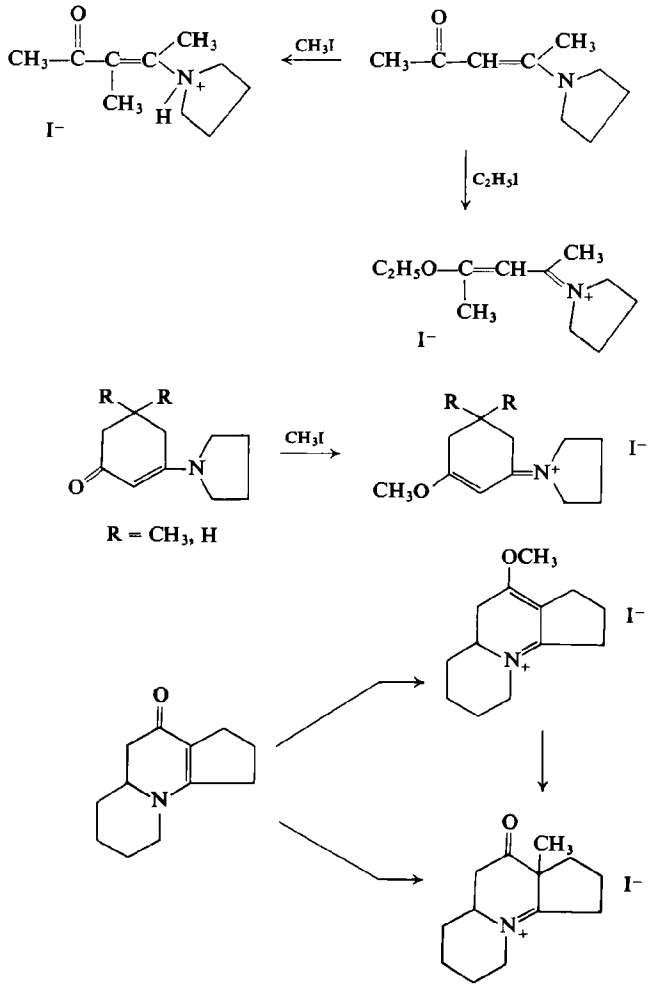
The use of branched secondary amines for enamine formation considerably favors the alkylation on carbon (*274,275*). Thermal rearrangement of quaternized products, obtained from the alkylations of enamines with allylic bromides, has also provided access to α-substituted aldehydes (*276*).



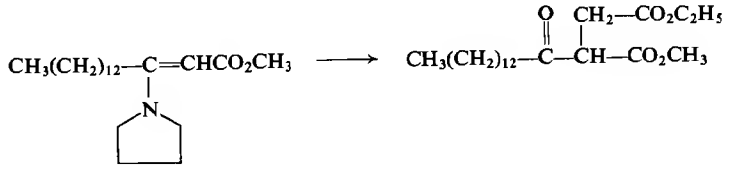
Quaternization of the enamine has been the more frequent result of alkylation reactions with cyclic enamines (*114,277–279*), but some successful carbon alkylations have been reported (*280–282*).

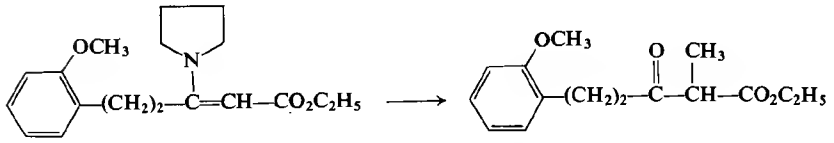


Vinylogous amides, which have an enamine function in conjugation with a carbonyl group, constitute tridentate systems and thus open the possibility of alkylation on carbon, nitrogen, or oxygen. It has been found that the pyrrolidine enamine of acetylacetone gives rise to a carbon methylation but an oxygen ethylation product (*41*). The alkylation of cyclic 1,3-diketone-derived enamines has been studied (*41,283*). O Alkylation was found in alcohol solvents and predominant C alkylation in nonprotonic solvents.

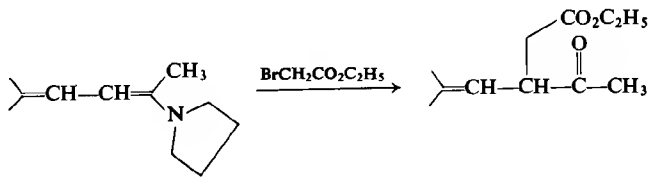


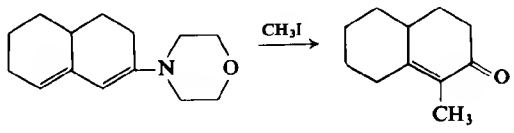
Enamine derivatives have also found use in the alkylation of β-keto-esters. Greater selectivity for monoalkylation products and consequently greatly improved yields have been reported (*284–287*).

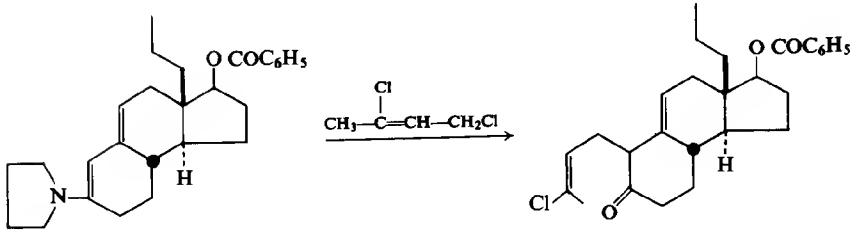




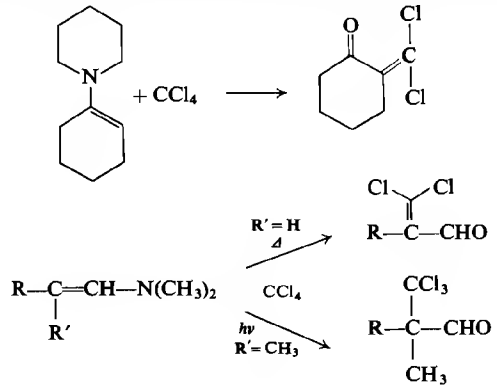
Alkylation of dienamines with alkyl halides has been found to take place at the α carbon (*288–290*). The reaction was used in the synthesis of steroid analogs (*291*).



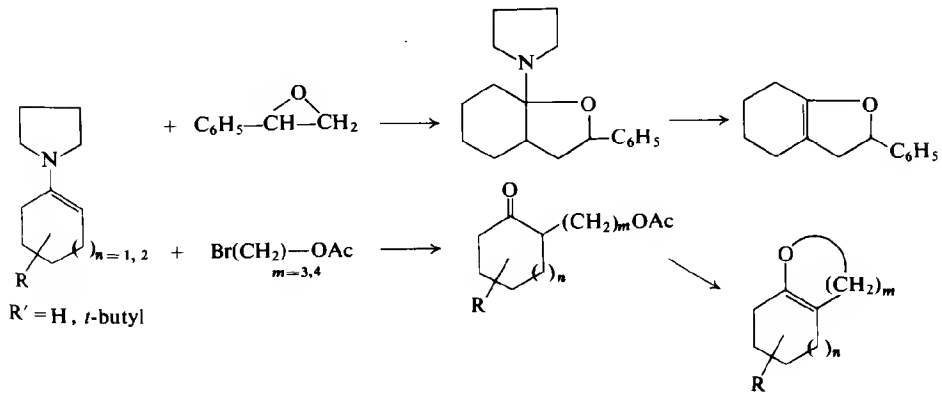


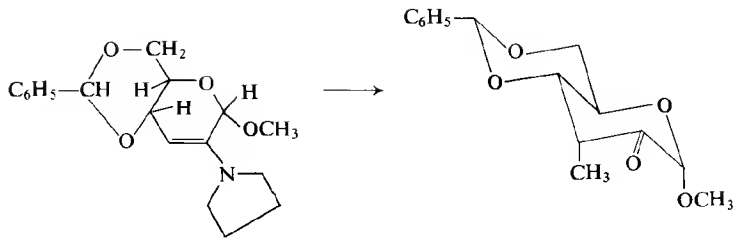


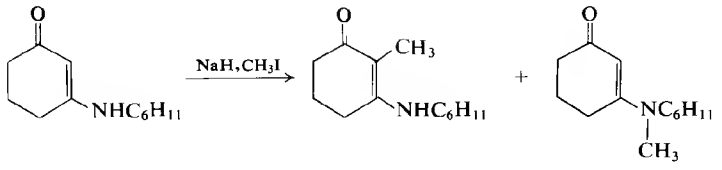
The α alkylation of enamines has also been extended to photochemical and thermal reactions of carbon tetrachloride with enamines (*292,293*).

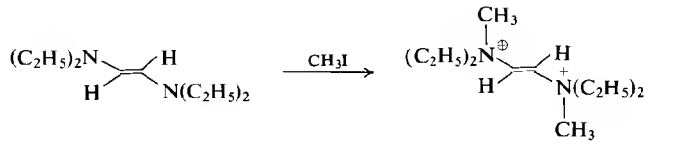


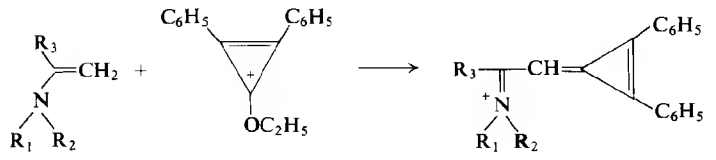
Alkylation of enamines with epoxides or acetoxybromoalkanes provided intermediates for cyclic enol ethers (*668*) and branched chain sugars were obtained by enamine alkylation (*669*). Sodium enolates of vinylogous amides underwent carbon and nitrogen methylation (*670*), while vicinal endiamines formed bis-quaternary amonium salts (*647*). Reactions of enamines with a cyclopropenyl cation gave alkylated imonium products (*671*), and 2-benzylidene-3-methylbenzothiazoline was shown to undergo enamine alkylation and acylation (*672*). A cyclic enamine was alkylated with methylbromoacetate and the product reduced with sodium borohydride to the key intermediate in a synthesis of the quebrachamine skeleton (*673*).

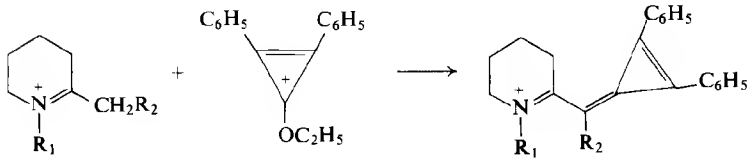


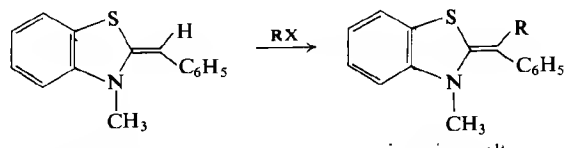






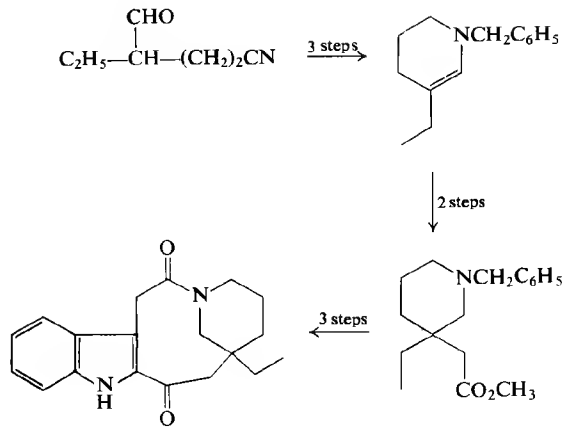






R = CH_3
CH_3CO
ArCO
2,4-$C_6H_3(NO_2)_2$

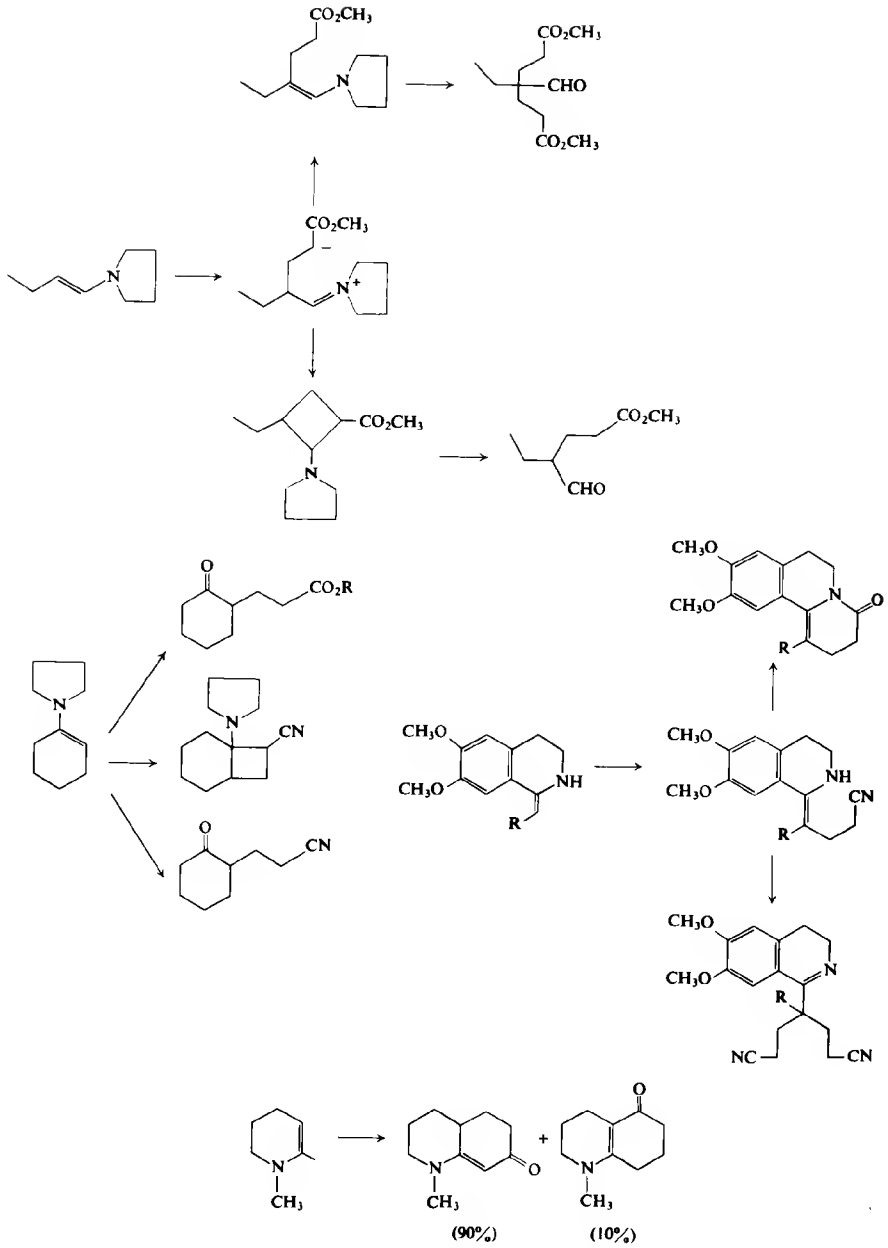
imonium salt
R = CH_3



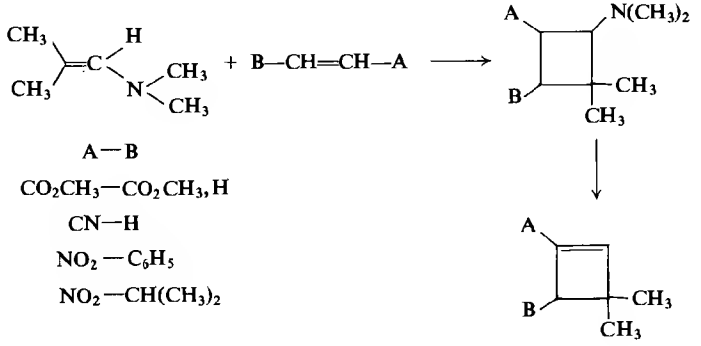
B. By Michael Addition Reactions

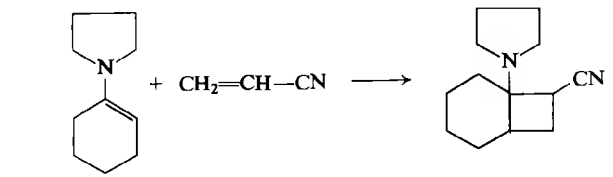
The problem of nitrogen alkylation of enamines, which one encounters with alkyl halides, is of no consequence in alkylations with positively activated olefins, since the generation of amonium salts can be expected to be reversible in these cases. Thus such enamine alkylations are obviously attractive to the synthetic chemist. Their particular importance, however, arises from avoidance of the serious obstacles often found with parallel enolate anion reactions.

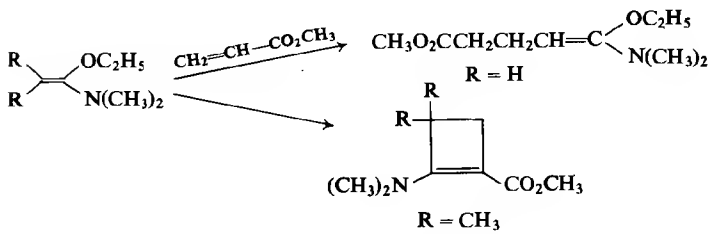
Thus the reactions of cyclic or acyclic enamines with acrylic esters or acrylonitrile can be directed to the exclusive formation of monoalkylated ketones (*3,294–301*). The corresponding enolate anion alkylations lead preferentially to di- or higher-alkylation products. However, by proper choice of reaction conditions, enamines can also be used for the preferential formation of higher alkylation products, if these are desired. Such reactions are valuable in the α substitution of aldehydes, which undergo self-condensation in base-catalyzed reactions (*117,118*). Monoalkylation products are favored in nonhydroxylic solvents such as benzene or dioxane, whereas dialkylation products can be obtained in hydroxylic solvents such as methanol. The difference in products can be ascribed to the differing fates of an initially formed zwitterionic intermediate. Collapse to a cyclobutane takes place in a nonprotonic solvent, whereas protonation on the newly introduced substitutent and deprotonation of the imonium salt, in alcohol, leads to a new enamine available for further substitution.



The facile formation of cyclobutane products is indeed another important contribution of enamine chemistry (*302–306*). The formation of cyclobutanes has also been found in the closely related reactions of amino acetal derivatives of ketenes with acrylic esters (*307*).

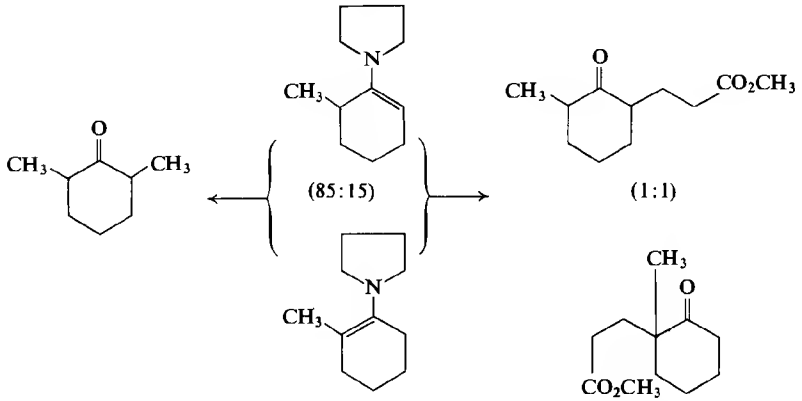




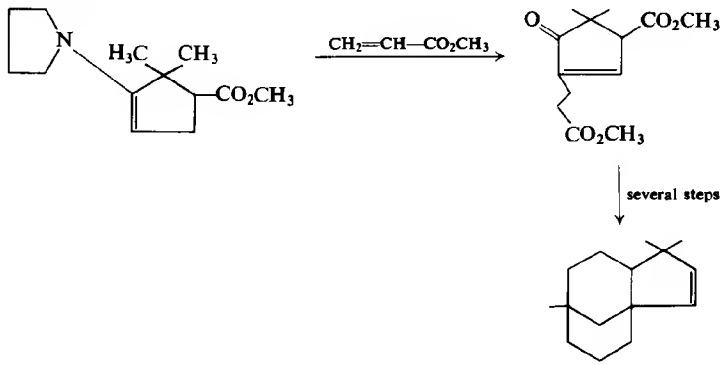


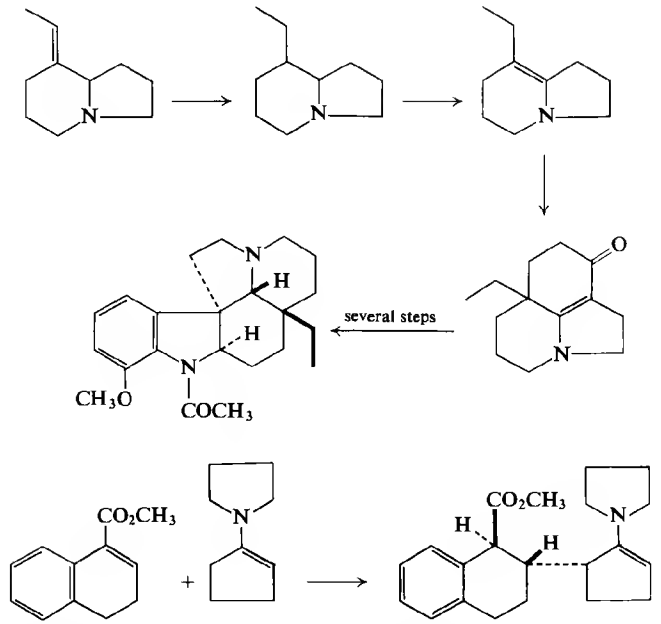
It is interesting to see that the addition of methyl acrylate to the pyrrolidine enamine derivative of 2-methylcyclohexanone in benzene gave equal amounts of 2-methyl-2-carbomethoxyethyl and 2-methyl-6-carbomethoxyethylcyclohexanone even though the less substituted double-bond isomer predominates in the starting enamine (*199,200,237*). In contrast, the methylation of the same enamine mixture led only to 2,6-dimethylcyclo-

hexanone (*237*). This result suggests a higher steric requirement for the acrylic ester as compared with methyliodide in a transition state, which involves generation of a 1,3-diaxial interaction with the electrophile (*235*). However, in ethanol, only 2,6-substituted products are formed (*3*).

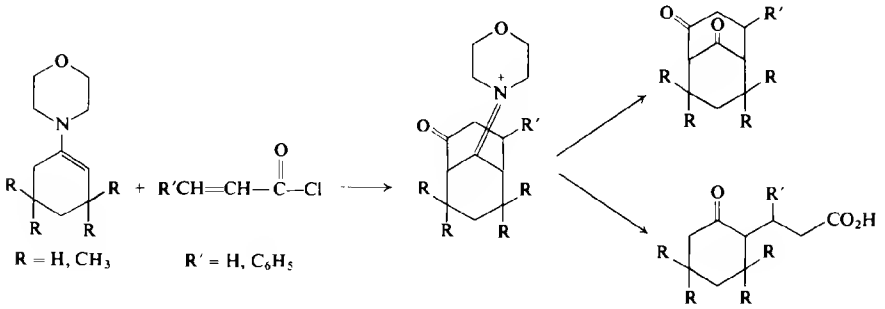


The formation of an enamine from an α,α-disubstituted cyclopentanone and its reaction with methyl acrylate was used in a synthesis of clovene (*308*). In a synthetic route to aspidospermine, a cyclic enamine reacted with methyl acrylate to form an imonium salt, which regenerated a new cyclic enamine and allowed a subsequent internal enamine acylation reaction (*309,310*). The required cyclic enamine could not be obtained in this instance by base isomerization of the allylic amine precursor, but was obtained by mercuric acetate oxidation of its reduction product. Condensation of a dihydronaphthalene carboxylic ester with an enamine has also been reported (*311*).



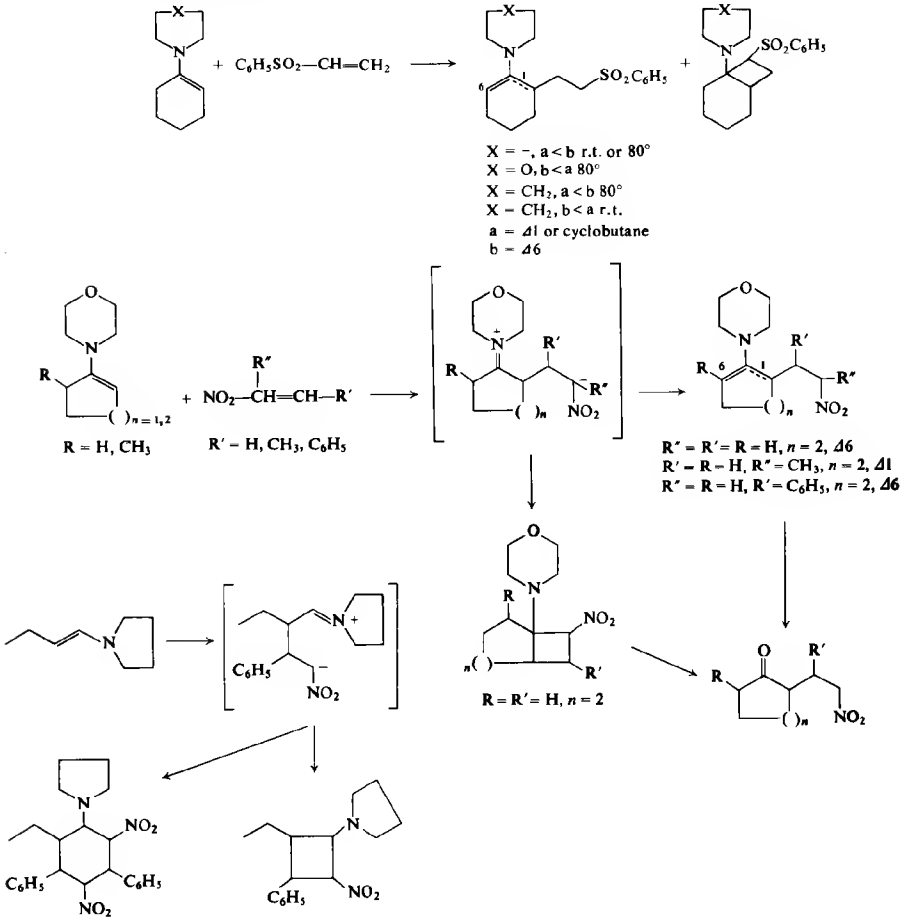


The reactions of enamines with α,β-unsaturated acid chlorides have provided bridged bicyclic diketones (*312,313*).

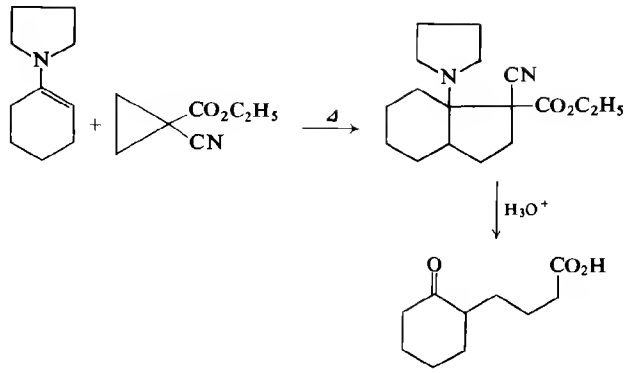


Unsaturated sulfones (*314,315*) and nitroolefins (*303,315–317*) also give alkylation products with enamines. In the latter reactions the formation of nitroethyl or cyclobutane derivatives has been found (*316*) to depend on the reaction medium as well as steric and electronic parameters which determine the fate of zwitterionic intermediates. Thus no enamine products could

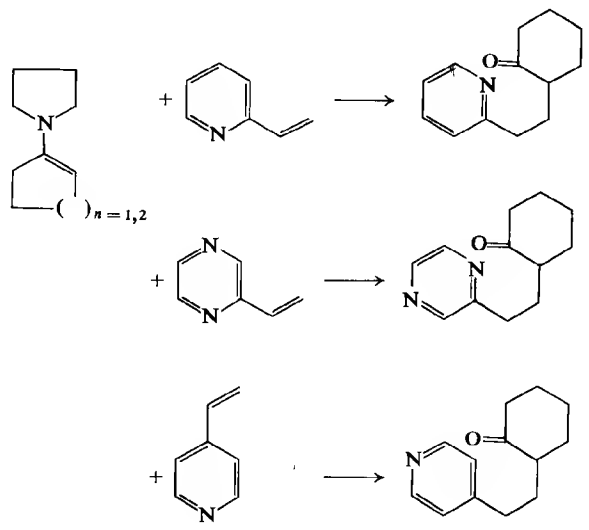
be obtained from reactions with aldehyde derived enamines and attempts to trap such compounds by double alkylation in protonic solvents led instead to condensation of the zwitterionic intermediate with a second equivalent of nitroolefin.



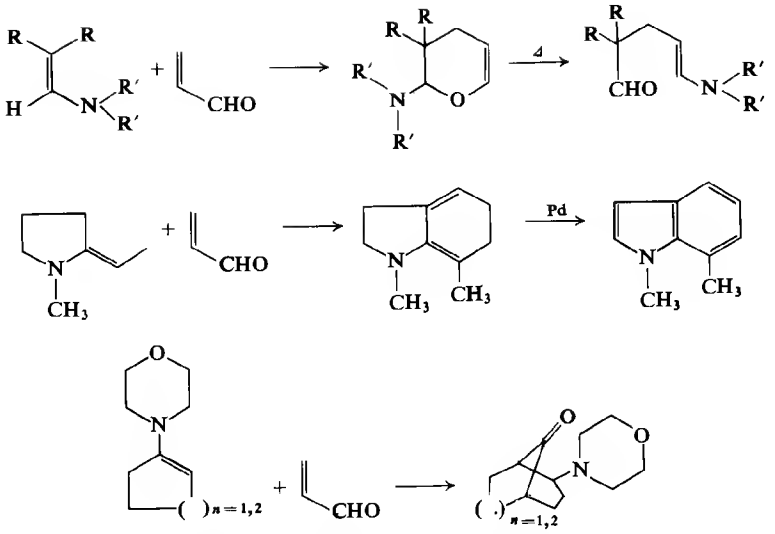
A reaction related to the Michael addition reactions of enamines to unsaturated esters, which leads to δ-ketoesters, is the reaction with 1-carbethoxy-1-cyanocyclopropane (*318*). This gives access to ketones substituted with the next higher homologous acid chain.



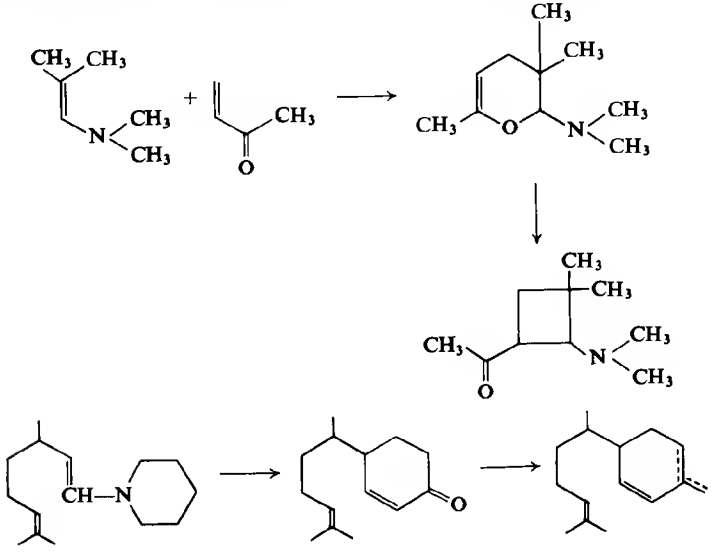
The alkylation of enamines with 2- and 4-vinyl pyridines has also been described (*319*).

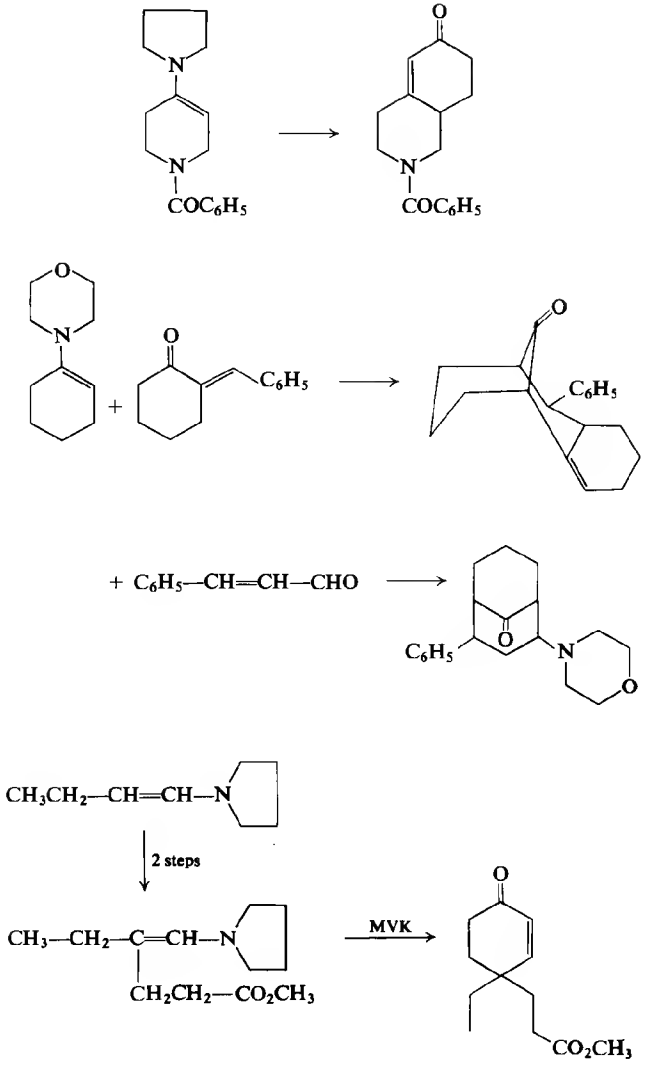


From the addition reactions of acrolein- to aldehyde-derived enamines, aminotetrahydropyrans have been obtained. On heating, these products rearranged to enaminoaldehydes in examples where the initial enamine was disubstituted (*320,321*). The addition of acrolein to ketone derived enamines has been applied to syntheses of heterocyclic and bridged bicyclic compounds (*301,321–323*).

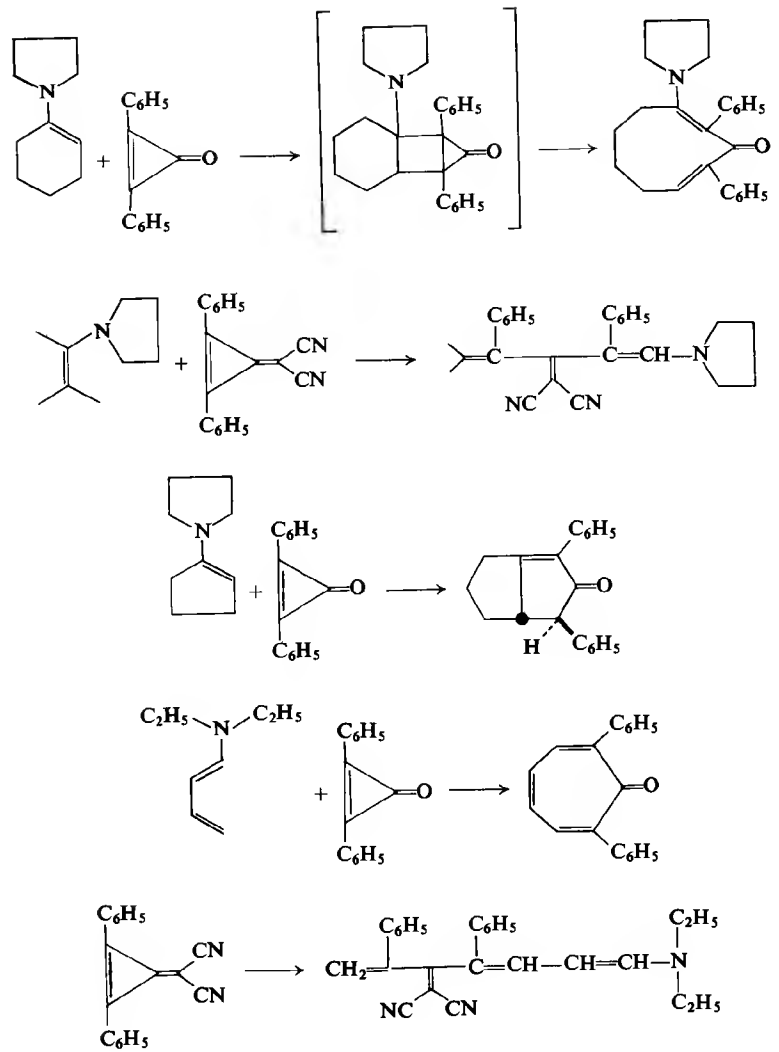


Similarly, methyl vinyl ketone has been added to enamines derived from aldehydes (*3,321,324–327*) and ketones (*3,328*), providing a useful extension of the Robinson annelation reaction. Condensations of enamines with other α,β-unsaturated ketones can give a variety of diketones (*329*).

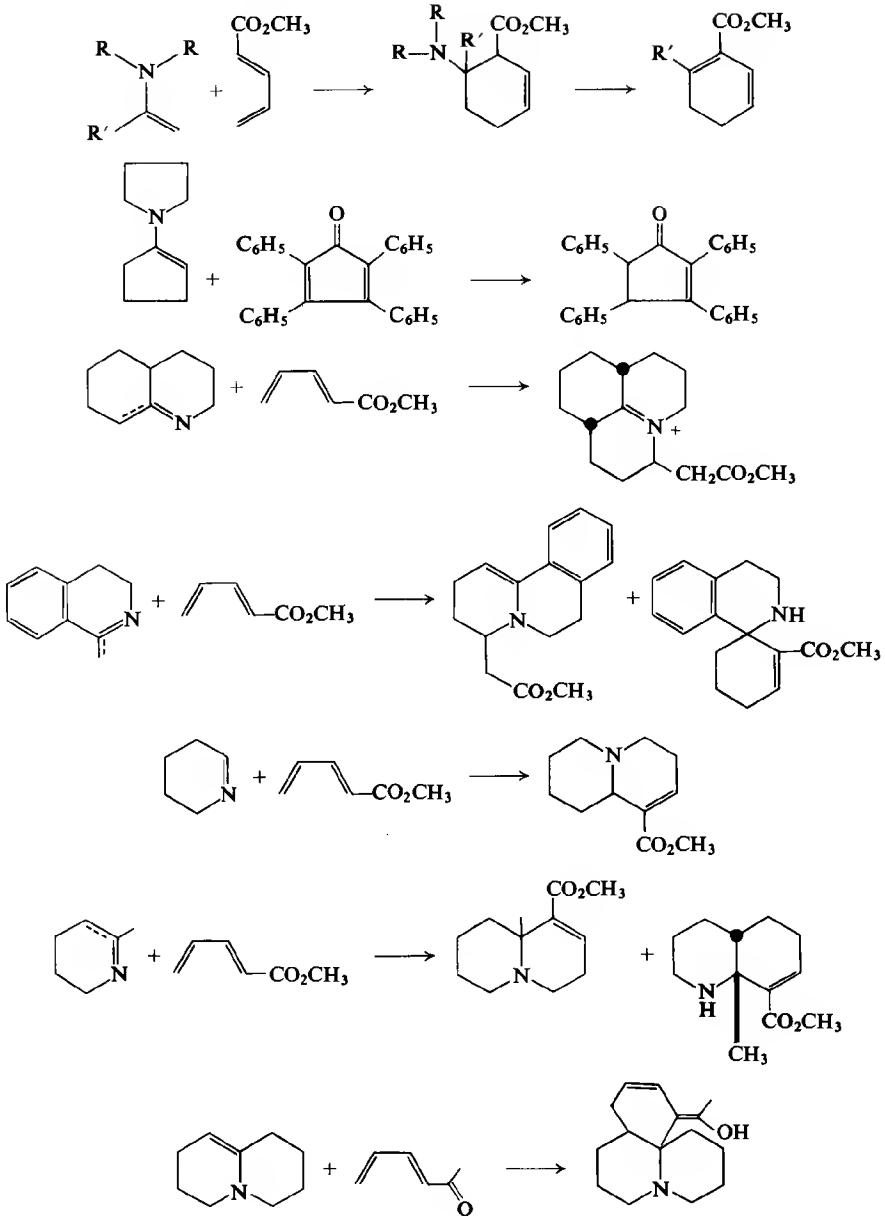




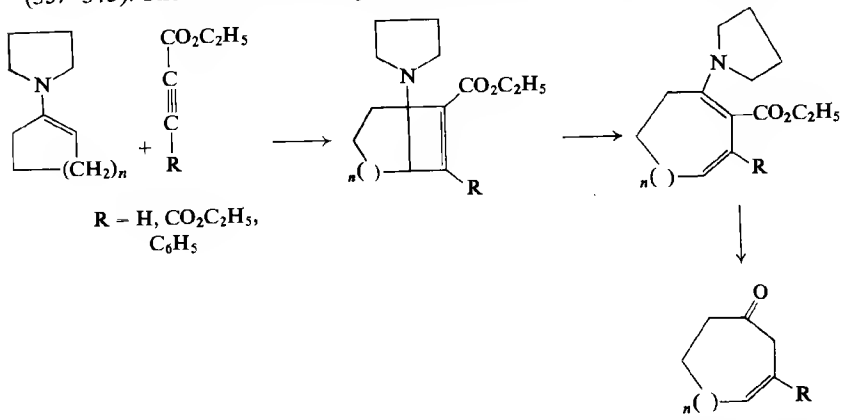
The addition of diphenylcyclopropenone to pyrrolidinocyclohexene and ring expansion of the adduct gave an aminocyclononadicnone (*330,331*), whereas the corresponding cyclopentanone derived enamine yielded a bicyclic enone.



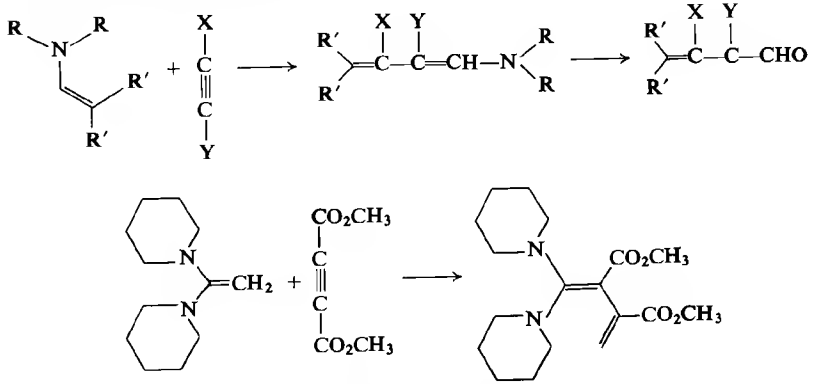
Formal Diels–Alder additions of dienesters (*111,332–335*) and dienketones (*336*) to enamines have provided synthetic paths which may be applied to some natural products syntheses. However, a reaction of tetracyclone (*330*) gave only the cyclopentenone, rather than a Diels–Alder adduct.



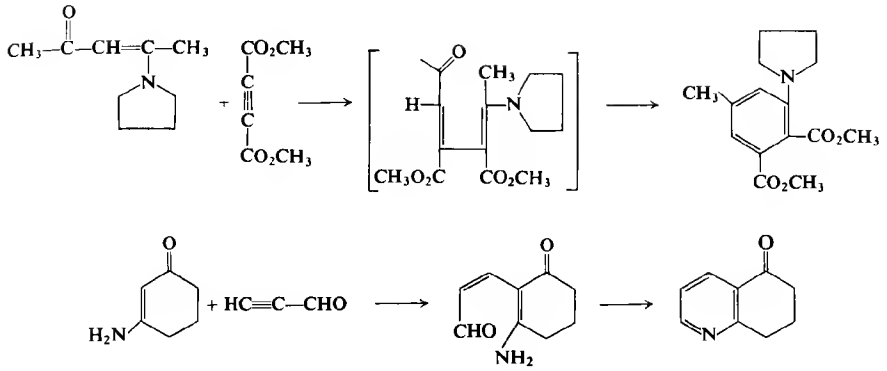
A two-carbon ring expansion of cyclic ketones was achieved by the addition of acetylenic esters and diesters to the enamine derivatives of the ketones, and reported almost simultaneously from several laboratories (*337–343*). The intermediate bicyclic adduct could be isolated in some cases.



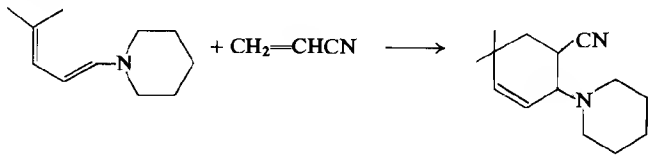
Additions to acyclic enamines (*337,343*), to 1,1-dipiperidinoethylene (*344*), and to the analogous ethoxydimethylaminoethylene (*344*) gave products derived from ring cleavage of an initially formed cyclobutene adduct.

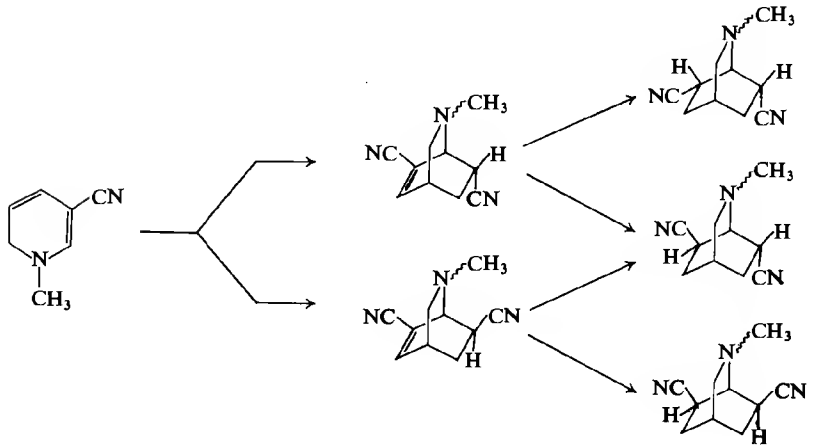


Dicarbomethoxyacetylene has also been added to the pyrrolidine enamine derivative of acetylacetone, demonstrating a new synthesis of phthalic esters (*345*). A 3-acylpyridine synthesis was achieved by the addition of an acetylenic aldehyde to the vinylogous amide derived from ammonia and dihydroresorcinol (*346*).

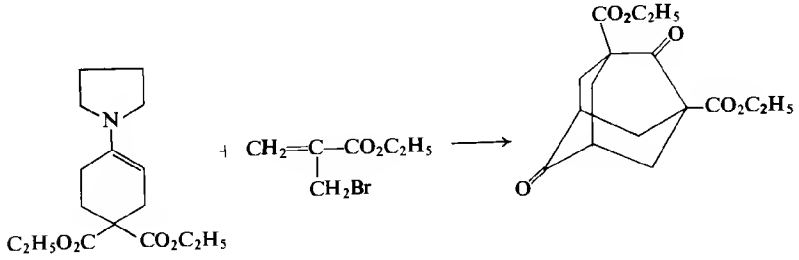


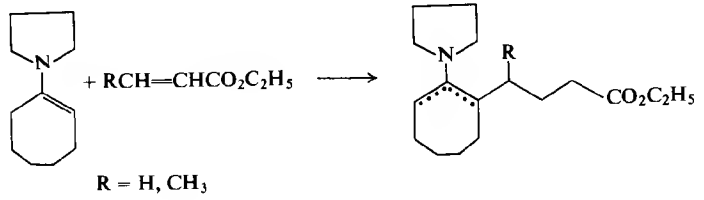
Positively activated olefins have also been condensed with dienamines derived from aldehydes (*321,330,347,348*) and ketones. Of special interest is the formation of bridged systems from homoannular dienes (*229–231*) which has been applied to the isoquinuclidine system of the iboga alkaloids (*137–140,349*).



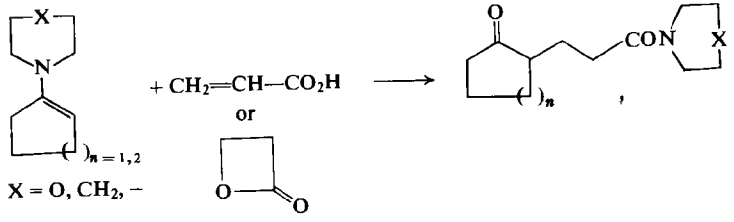


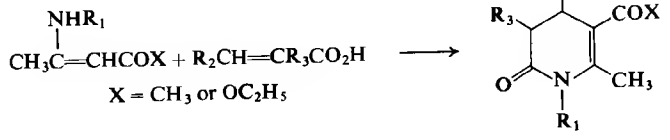
Enamine addition to an unsaturated ester, followed by an intramolecular alkylation, provided a facile synthesis of an adamantane bis-β-ketoester (*674*). Michael addition of pyrrolidinocycloheptene to other acrylic esters (*668*) and of other enamines to acrylic acids (*675*), a chloroacrylonitrile (*676*), and an unsaturated cyanocarboxamide (*677*) were reported.

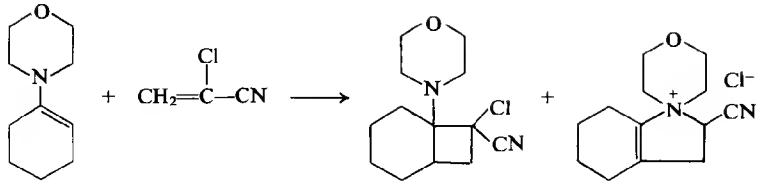


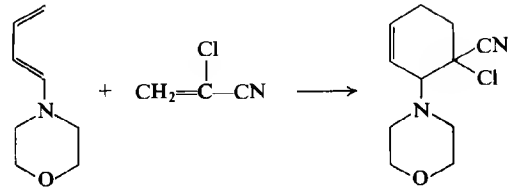


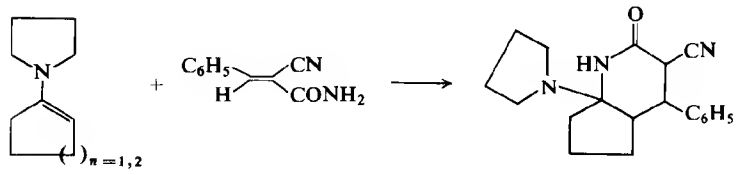
R = H, CH_3



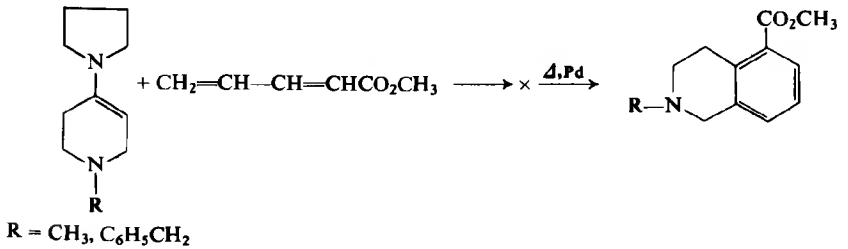




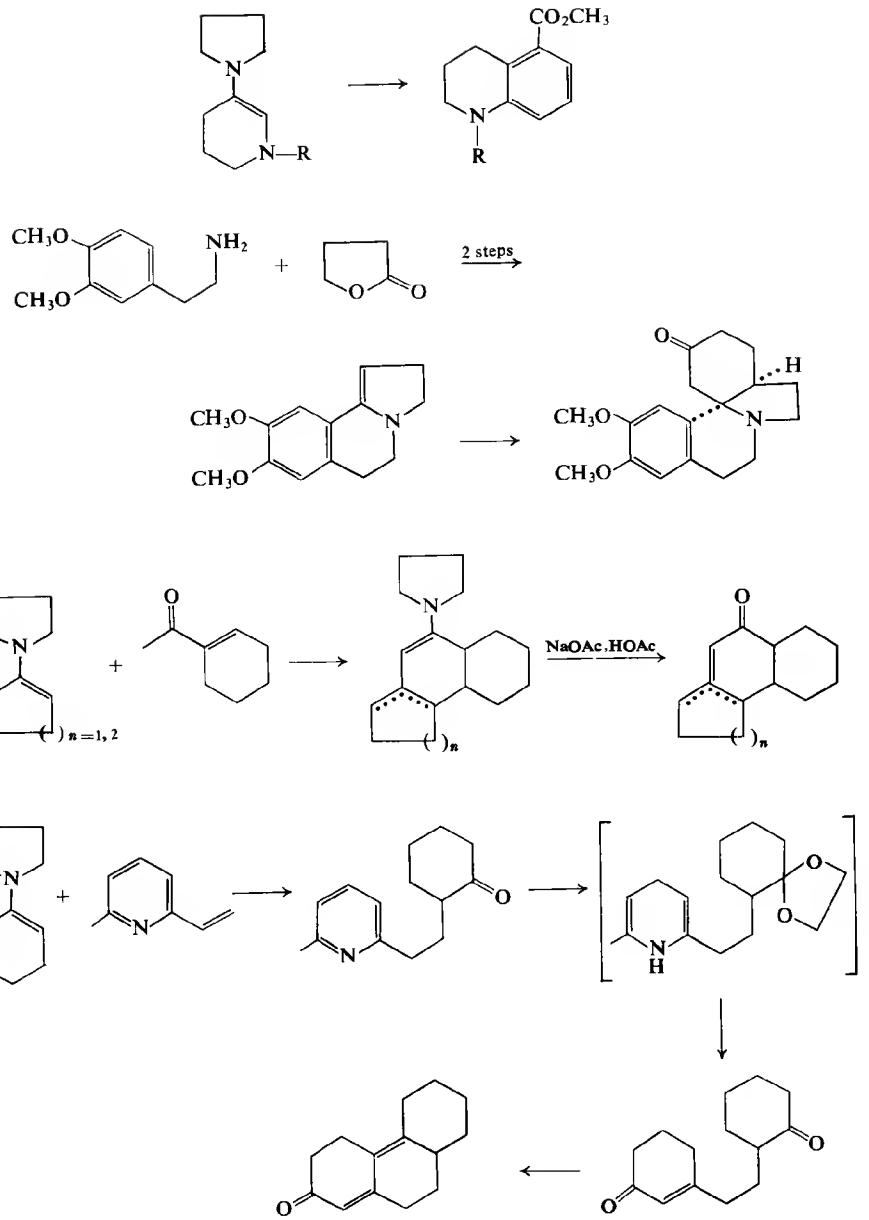




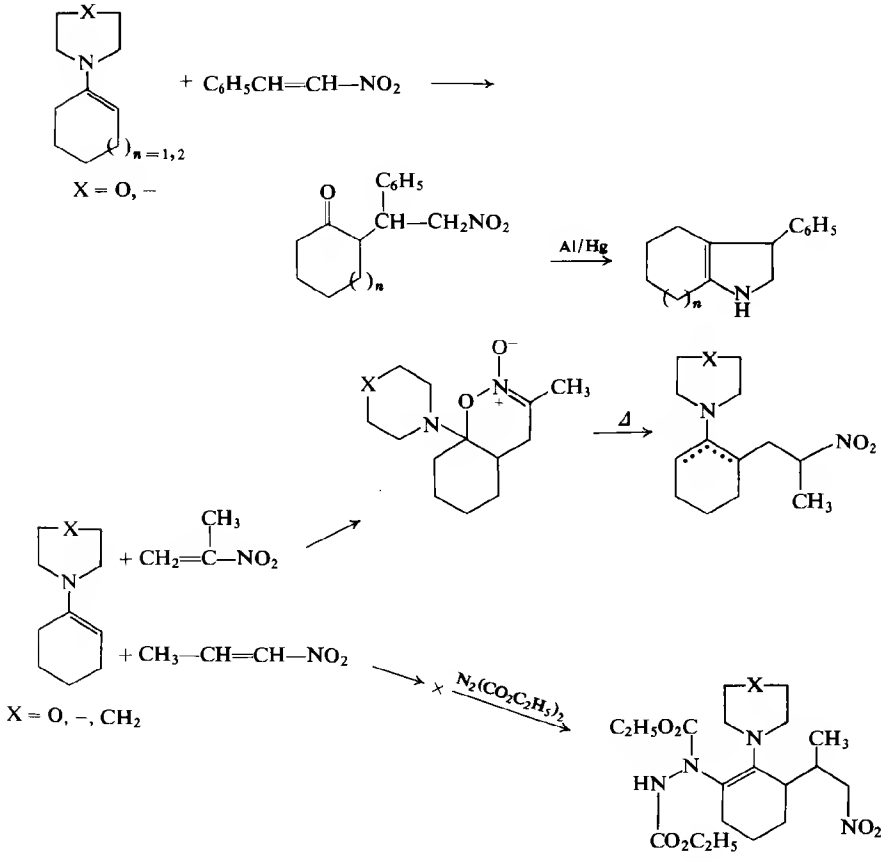
Reactions of 3- and 4-piperidone-derived enamines with a dienester gave intermediates which could be dehydrogenated to tetrahydroquinolines and tetrahydroisoquinolines (*678*). The methyl vinyl ketone annelation of pyrrolines was extended to an erythrinan synthesis (*679*). Perhydrophenanthrenones were obtained from 1-acetylcyclohexene and pyrrolidinocyclohexene (*680*) or alternatively from Birch reduction and cyclization of a 2-pyridyl ethyl ketone intermediate, which was formed by alkylation of an enamine with a 2-vinylpyridine (*681*).

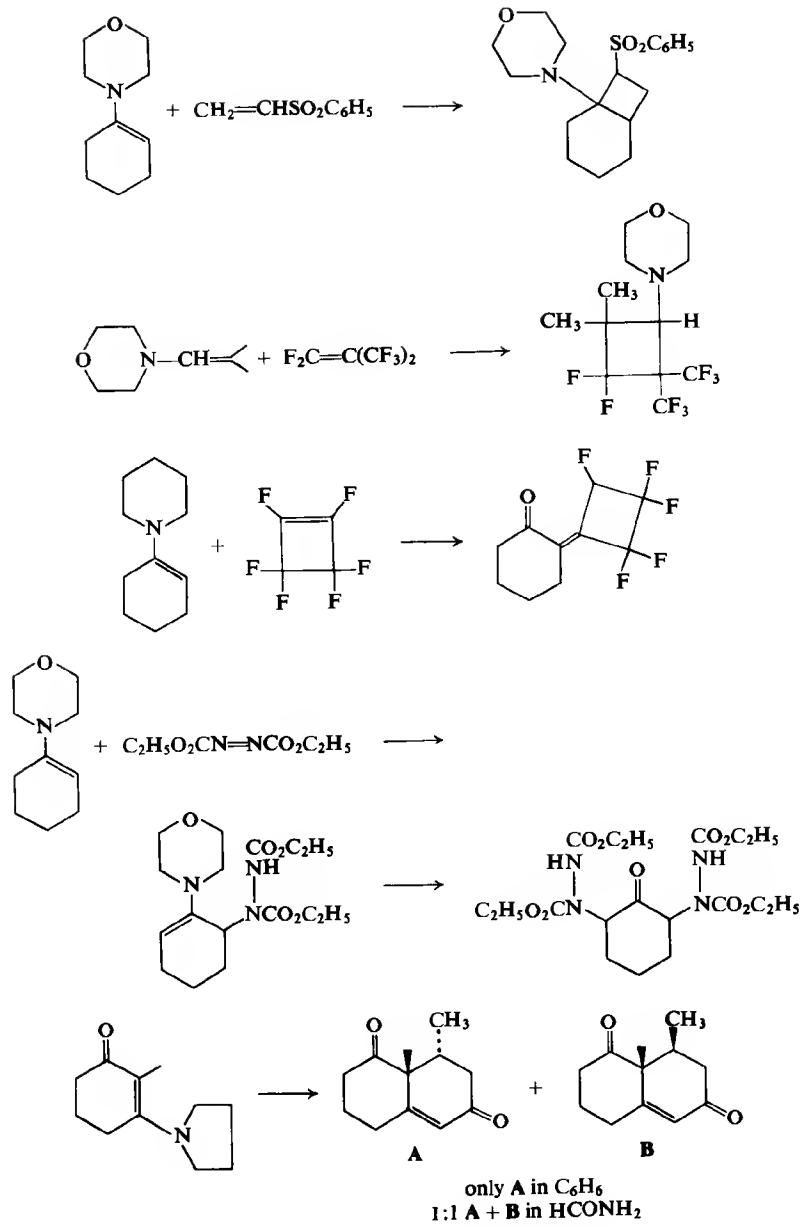


R = CH_3, $C_6H_5CH_2$



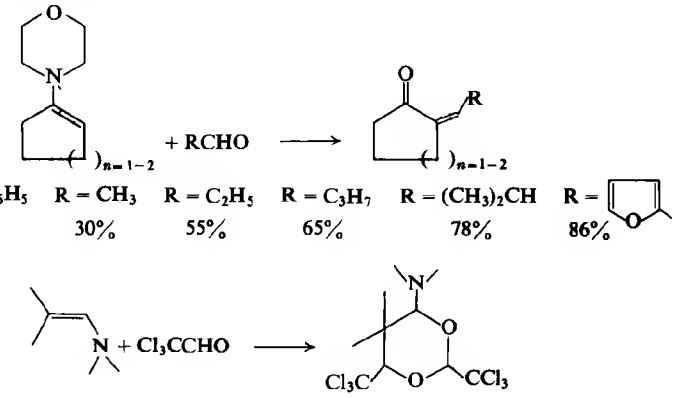
The alkylation of enamines with nitroolefins, which gives intermediates for reductive cyclization (*682*), also provided an example of a stable cyclization product derived from attack of the intermediate imonium function by the nitro anion (*683*). A previously claimed tetrasubstituted enamine, which was obtained from addition of a vinylsulfone to morpholinocyclohexene (*314*), was shown to be the corresponding cyclobutane (*684*). Perfluoroolefins also gave alkylation products with enamines (*685*). Reactions of enamines with diazodicarboxylate (*683,686*) have been used diagnostically for 6-substituted cyclohexenamines. In a reaction of 2-penten-4-one with a substituted vinylogous amide, stereochemical direction was seen to depend on solvent polarity (*687*).



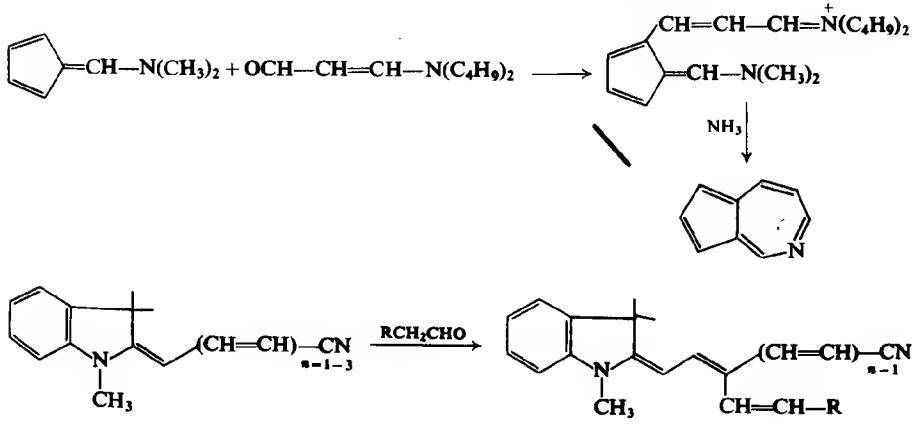


C. Condensations with Aldehydes and Ketones

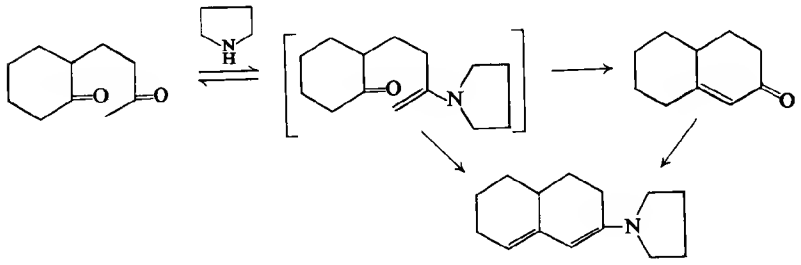
The reactions of enamines with aldehydes (*329,350*) are noteworthy in that they provide a route to the monobenzylidene derivatives of five- to seven-membered cyclic ketones as well as a method for the formation of other α,β-unsaturated carbonyl compounds, in fair to good yields. The condensation of benzaldehyde with enamines is also involved in the formation of 3,5-dibenzylpyridine from piperidine and benzaldehyde (*191–193*).



The condensation of a vinylogous formamide with an enamine has been applied to an aza azulene synthesis (*351*). The point of attachment of the aldehyde to the enamine in condensations with indolenin derived polyenamines was found to favor the second double bond (*352,353*).

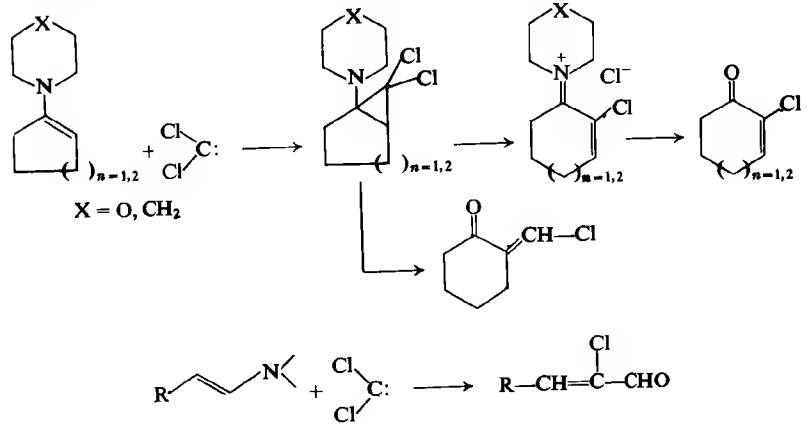


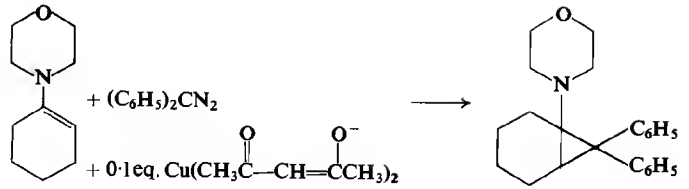
The long known catalyses of some ketone condensation reactions by secondary amines, can be postulated to have their basis in the reactions of enamine intermediates with ketones. The unsuitability of methyl ketones for azeotropic enamine formation is based on this phenomenon. Recent studies in cyclization reactions have added further support to this concept (*354*).

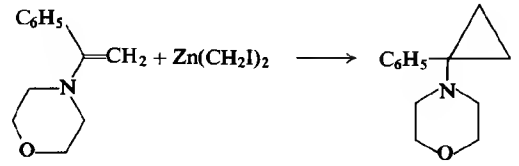


D. Reactions of Enamines with Divalent Carbon and Related Reactions

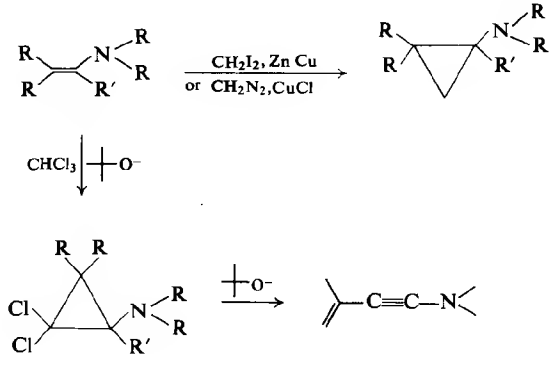
The reactions of dichlorocarbene with morpholine and piperidine enamines derived from cyclopentanone and cyclohexanone have been reported to lead to ring expanded and α-chloromethylene ketone products (*355,356*). Similarly α-chloro-α,β-unsaturated aldehydes were obtained from aldehyde derived enamines (*357*). Synthesis of aminocyclopropanes (*358,359*) could be realized by the addition of diphenyldiazomethane (*360*) and the methylene iodide–zinc reagent to enamines (*361*).





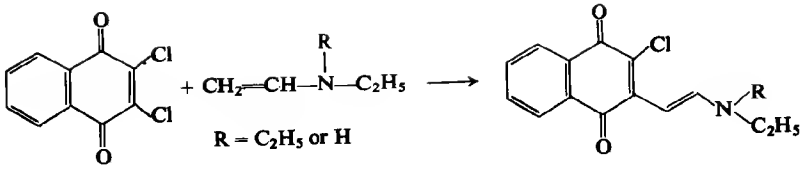


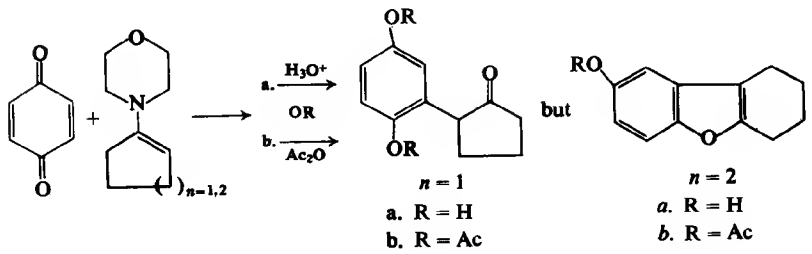
Aminocyclopropanes were prepared from enamines by the addition of Simmons–Smith reagent (*688*) or best through the cuprous-chloride-promoted decomposition of diazomethane (*689*). The reaction of an enamine with chloroform and base and opening of the resultant aminocyclopropane to an ynamine was reported (*690*).

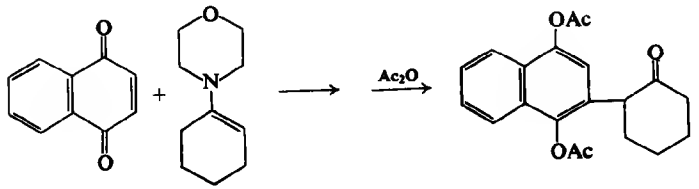


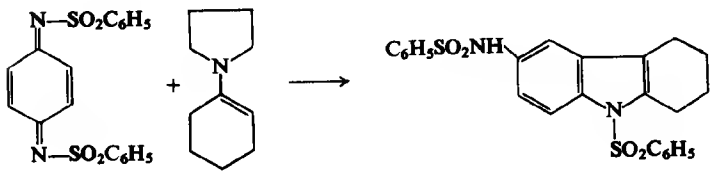
VI. Arylation of Enamines

The reactions of enamines with positively activated olefins have been extended to arylations with *p*-quinones (*350,362–369*) and quinone sulfonimides (*365–368,370*). Thus a new pathway for the facile formation of benzofurans and indoles became available.

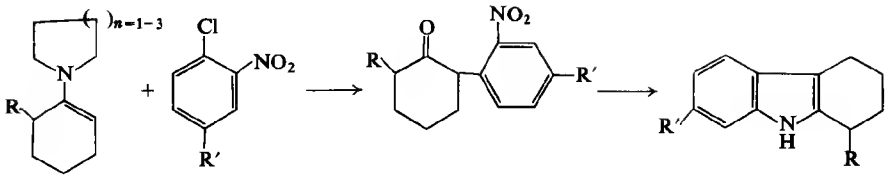






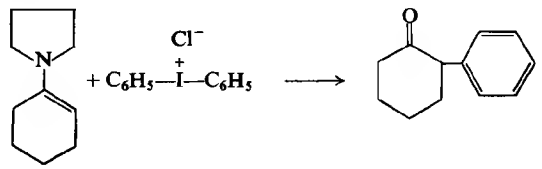


In the arylations of enamines with very reactive aryl halides (*352,370*) such as 2,4-dinitrochlorobenzene, the closely related mechanistic pathway of addition of the enamine to the aromatic system, followed by elimination of halide ion, can be assumed. The use of *o*-nitroarylhalides furnishes compounds which can be converted to indolic products by reductive cyclization. Less reactive aryl halides, such as *p*-nitrochlorobenzene, lead only to N-arylation or oxidation products of the enamines under more vigorous conditions.

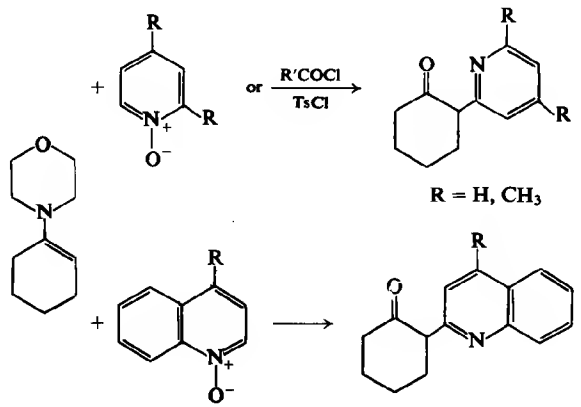


R = H, CH_3 R′ = NO_2, CO_2CH_3

Diaryliodonium salts also reacted with enamines to give α-aryl ketones in low yields (*370*).

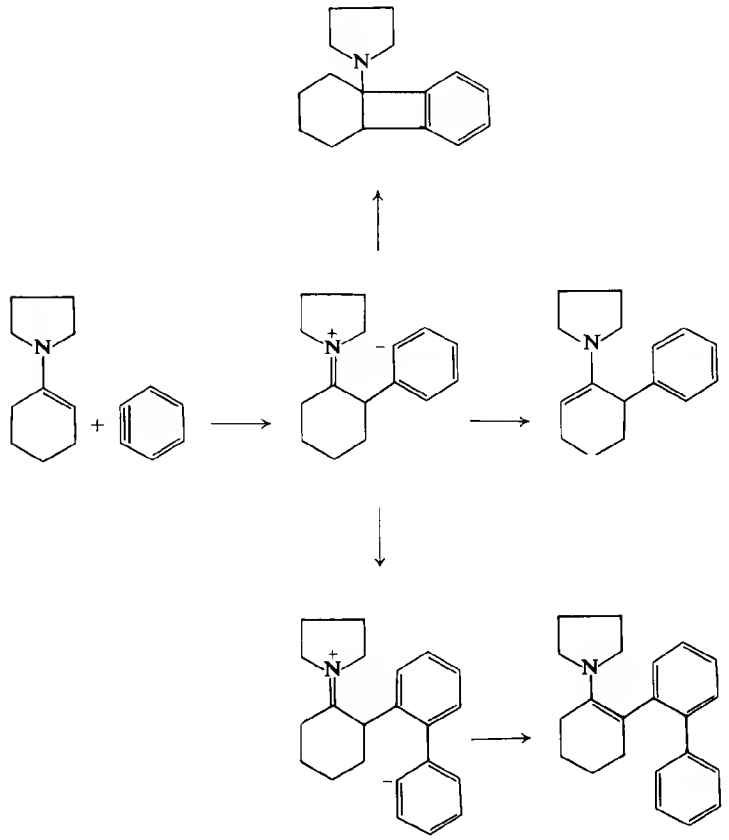


While pyridine and quinoline N-oxides do not react directly with enamines, they have been found to form α-pyridyl and 2-quinolinyl-2′-cyclohexanones in good yields after prior acylation (*371,372*).



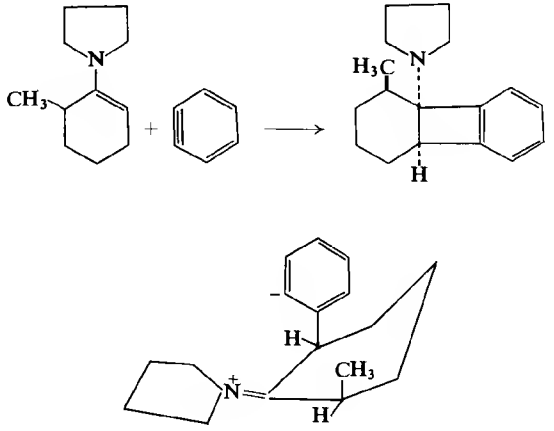
In the reactions of benzyne with enamines, arylated enamines or aminobenzocyclobutenes can be obtained, depending on reaction conditions and the structure of the enamine. Thus the presence of a proton source such as a secondary amine will favor the enamine product through capture of the zwitterionic intermediate, whereas in the absence of protons one sees

increased collapse of the intermediate to a benzocyclobutene. In addition to the simple phenylation products, one also encounters a small yield of *o*-biphenyl-substituted conjugated enamine (*22*). This may arise either from reaction of the zwitterionic intermediate with benzyne or from a reaction of the enamine with a coupling product of benzyne. Significantly, the zwitterionic biphenyl product leads to the conjugated enamine. This points to an intramolecular transfer of the α proton of the imonium salt.

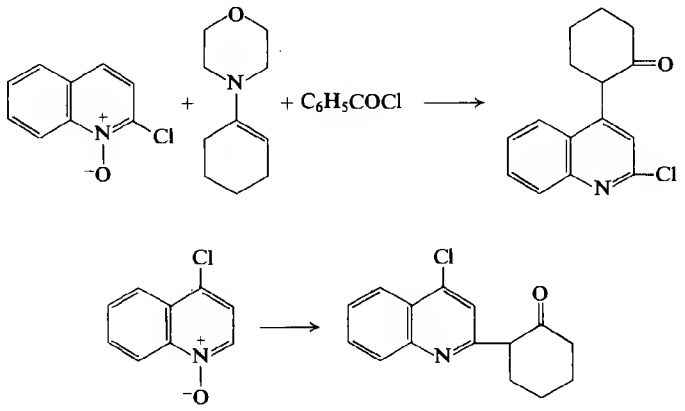


The presence of an α′ substituent, found in the pyrrolidine enamine of 2-methylcyclohexanone, blocks the possibility of an intramolecular proton transfer in the zwitterionic intermediate and thus only the benzocyclobutane

is formed in this reaction. This result provided the first direct support for the requirement of axial α attack and axial orientation of an α′ substituent in the transition state of electrophilic attack on a cyclohexenamine, with formation of a carbon-to-carbon bond (*22*).

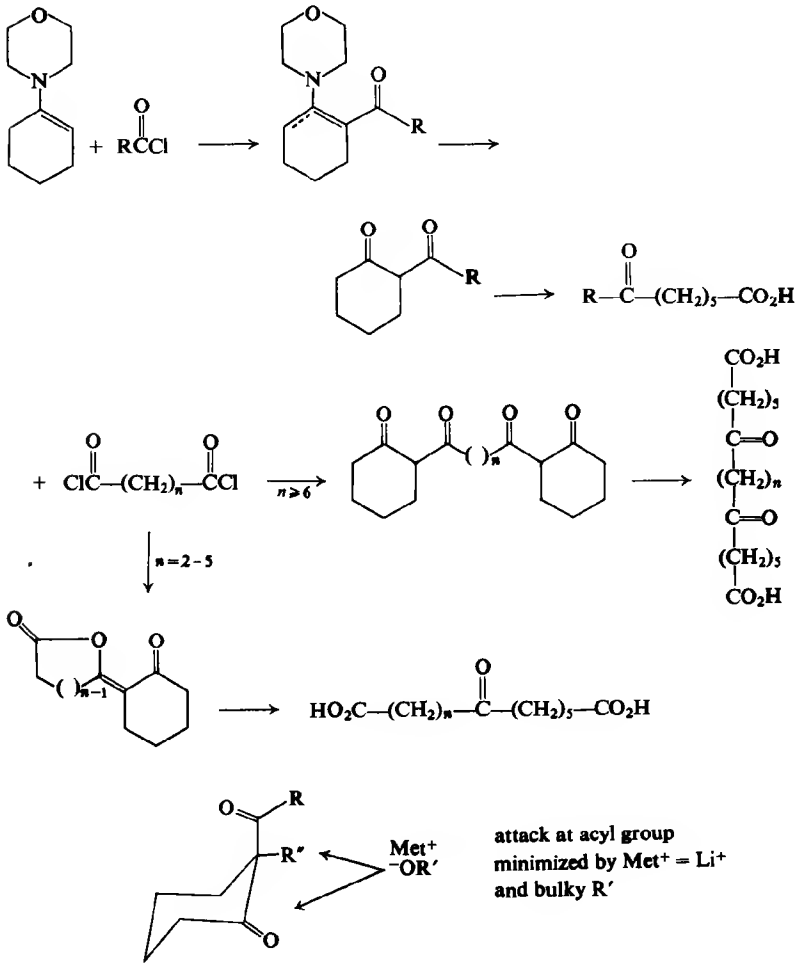


The arylation of morpholinocyclohexene with 2- or 4-chloroquinoline N-oxide or 4-chloropyridine N-oxide and benzoyl chloride led to cyclohexanone α-substituted with the respective chloroquinolines or 4-chloropyridine (*691*). 2,4-Dinitrofluorobenzene reacted with 2-benzylidene-3-methylbenzothiazoline to give the enamine arylation product (*672*).

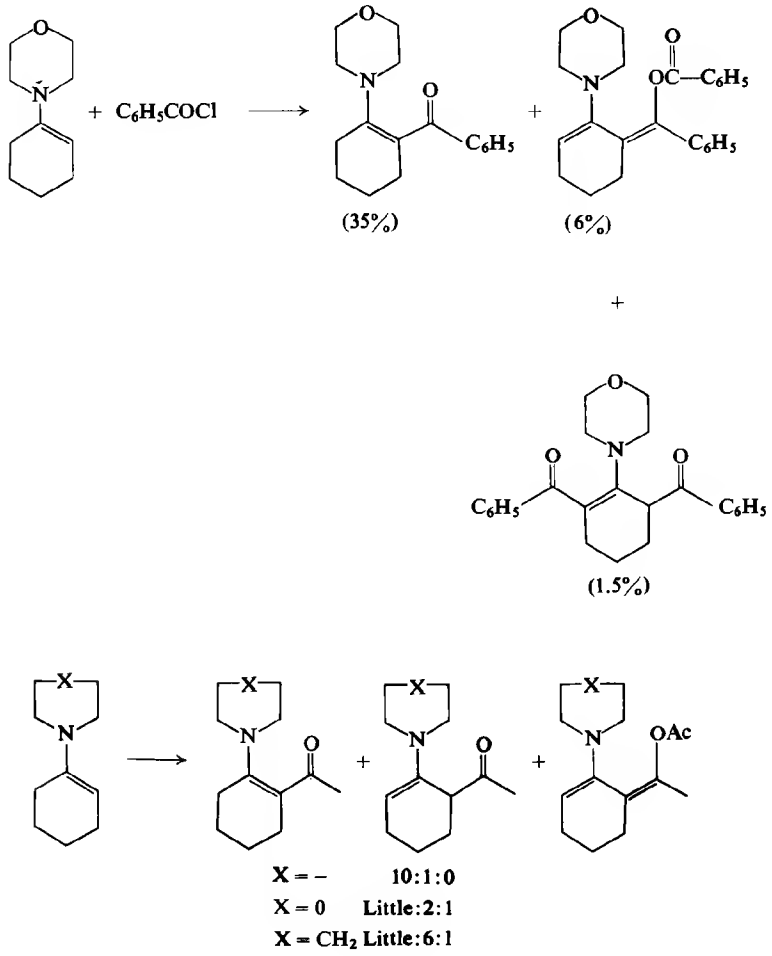


VII. Acylation of Enamines

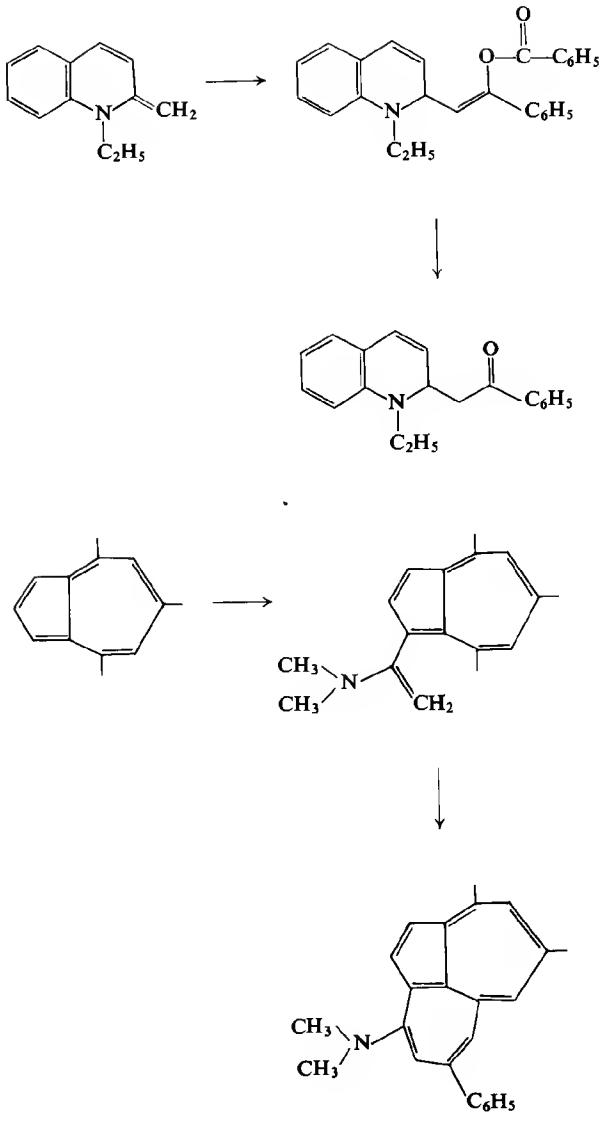
One of the most actively investigated aspects of enamine chemistry has been the acylation process (*1*). Initial intensive studies by Hünig (*373–375*) showed the ease of preparing a variety of β-diketones and particularly the synthetic potential of acylated cyclic ketones as intermediates in the preparation of aliphatic keto acids, keto dicarboxylic acids and diketo dicarboxylic acids (*376–378*).



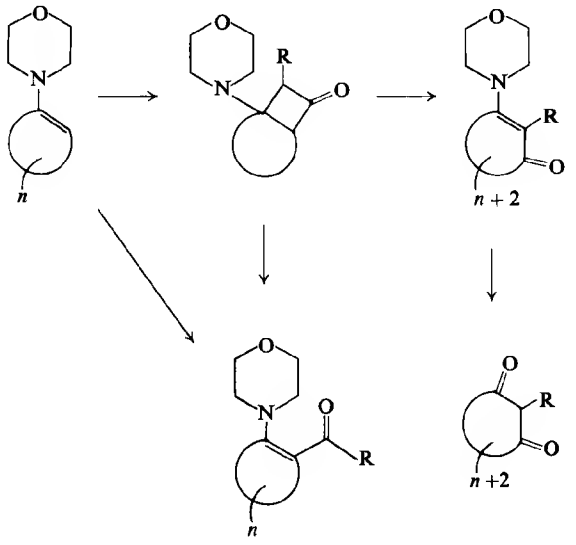
From the outset, the further O acylation of the initial ketonic products was recognized. Detailed studies have been made of the benzoylation of morpholinocyclohexene (*379–382*) and of the effect of the amine moiety of cyclohexanone derived enamines on the ratio of products (*383*) obtained from acylations.



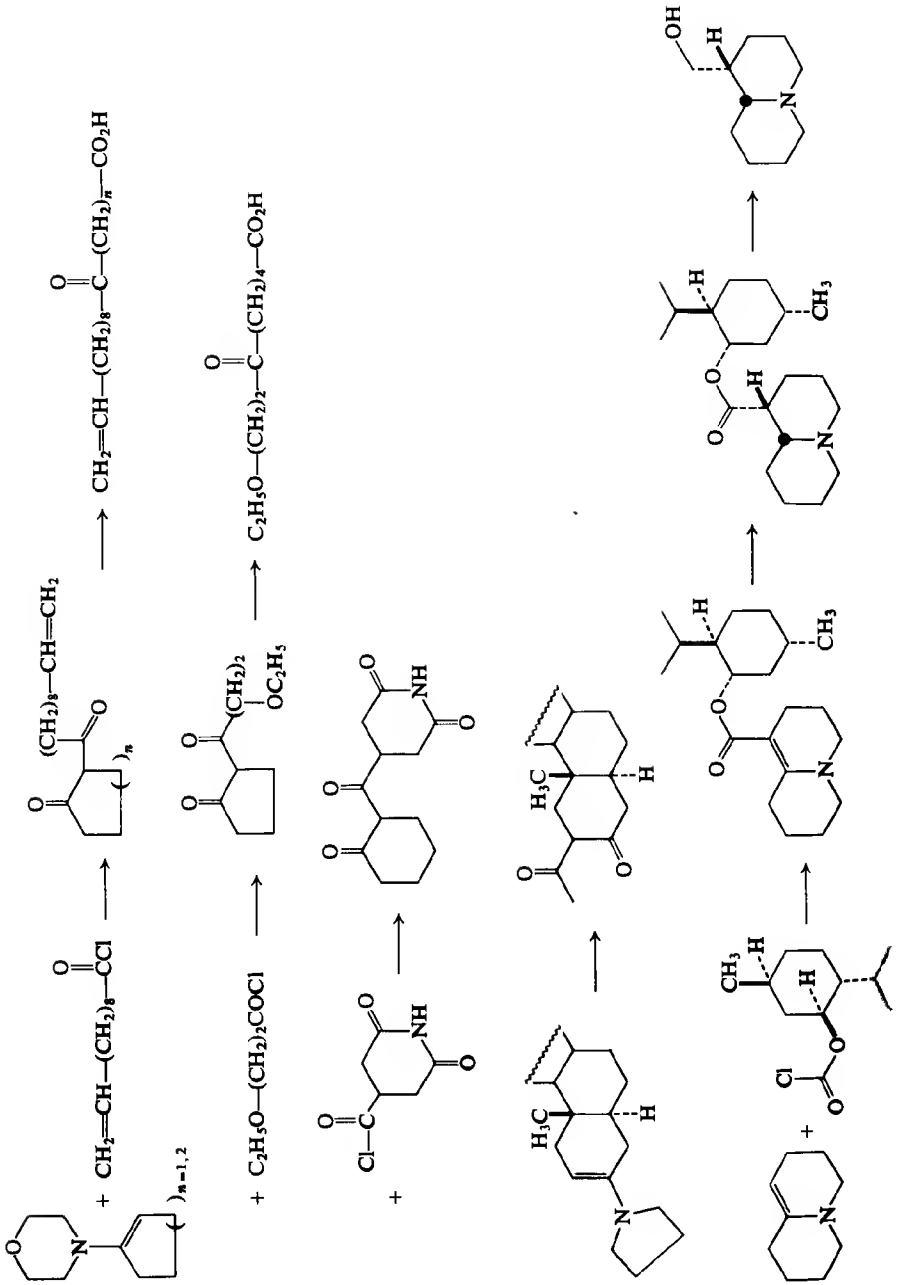
The benzoylation reaction was applied to cyclic enamines (*384*) and the synthesis of a heptazulene (*385*).



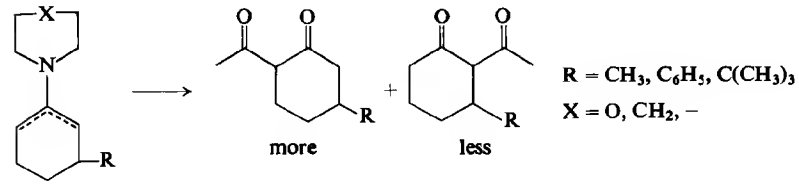
Most enamine acylations have been carried out with triethylamine as an auxiliary base to prevent salt formation and consequent removal of an equivalent amount of enamine from the reaction medium. It could be shown that acylations by this method proceed through an initial generation of ketene, which acts as the acylating agent. When excess morpholine enamine was used as the auxiliary base, ketene was not formed and direct acylation by the acid chloride was observed. This difference in reaction paths was found to be of particular importance in the acylation of eleven-, twelve-, and thirteen-membered-ring morpholine enamines, which resulted in the formation of ring-expanded products to an extent of about 30% in the presence of triethylamine, but not when excess enamine was used to neutralize the generated hydrochloric acid (*386,387*). With nine- and ten-membered rings less than 1 and 2% of ring expansion was found.

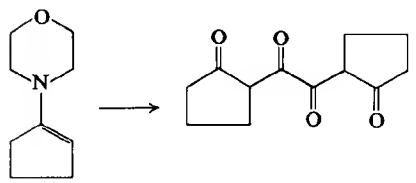


The acylation of enamines has been applied to the use of long-chain acid chlorides (*388*) and particularly to the elongation of fatty acids (*389–391*) and substituted aliphatic acids (*392*). The method has been used in the synthesis of the antineoplastic cycloheximide and related compounds (*393–395*) and in the acylation of steroids (*396*). Using an optically active chlorocarbonate, an asymmetric synthesis of lupinine could be achieved (*397*).

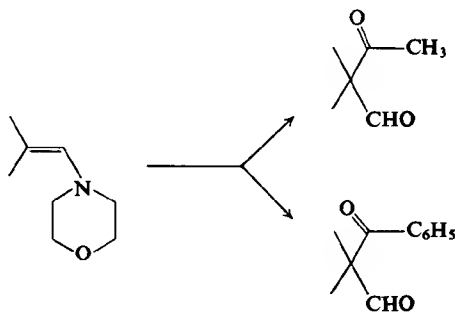


In the acylation of enamines derived from 3-substituted cyclohexanones, 6-acylated products were favored over 2-acylated products (*398*), thus revealing another selective enamine reaction sequence. The use of oxalyl bromide for the acylation of enamines has also been described (*399*).

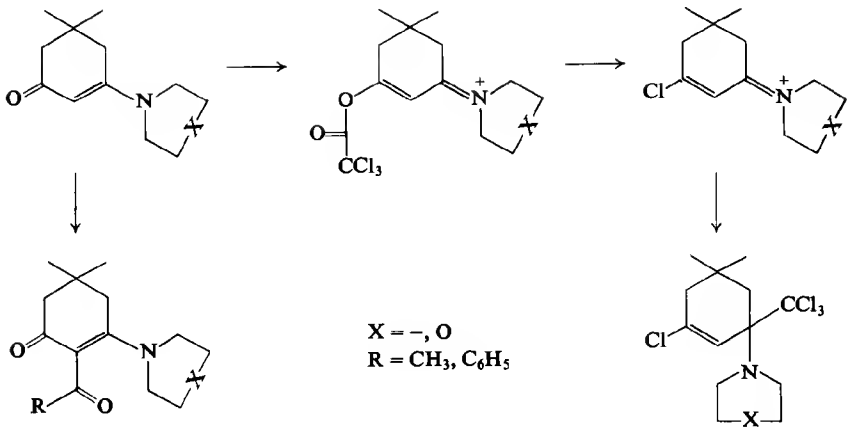




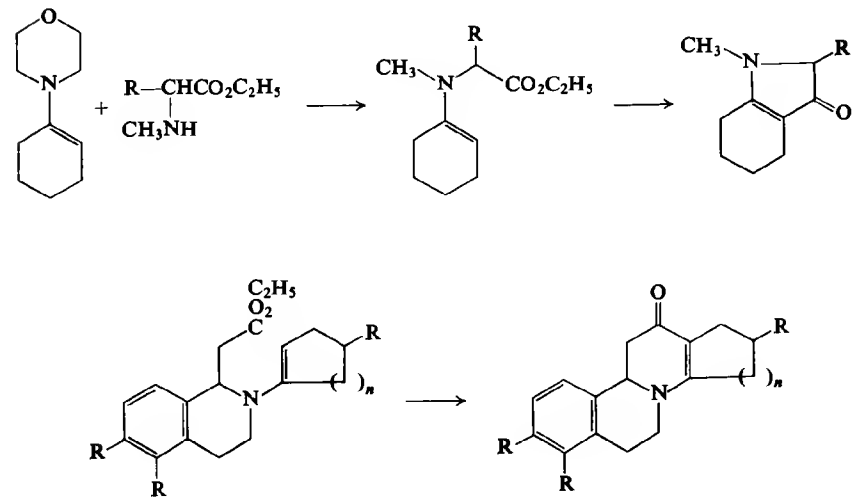
While most acylation and benzoylation studies have involved enamines derived from cyclic ketones, extensions to aldehyde derived enamines have also been successful (*400*).

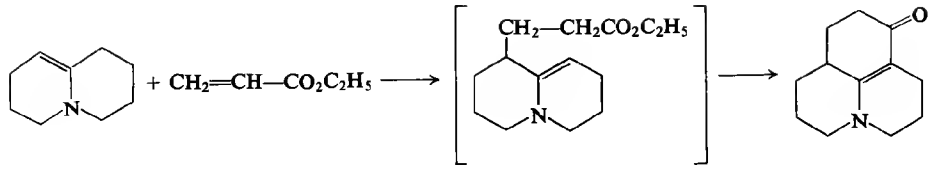


Acylation of the vinylogous pyrrolidine amide of dimedone with acetic anhydride or acetyl chloride led (possibly indirectly) to the carbon acylation product, whereas trichloroacetyl chloride gave rise to products derived from attack of chloride at the oxygenated double bond position in an initial O-acylation product (*401–404*).

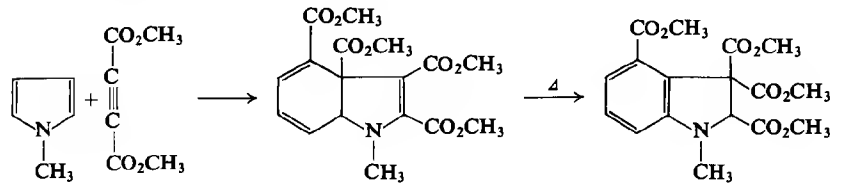


While esters do not usually react with enamines and can, in fact, be substituents in the azeotropic preparation of enamines, they can be used in acylation reactions when these involve intramolecular cyclizations. Such reactions have been observed even at room temperature when they lead to the formation of five- and six-membered vinylogous lactams (*362*). Applications to precursors for azasteroids (*405*) and alkaloids (*309,406*) are key steps in synthetic sequences.

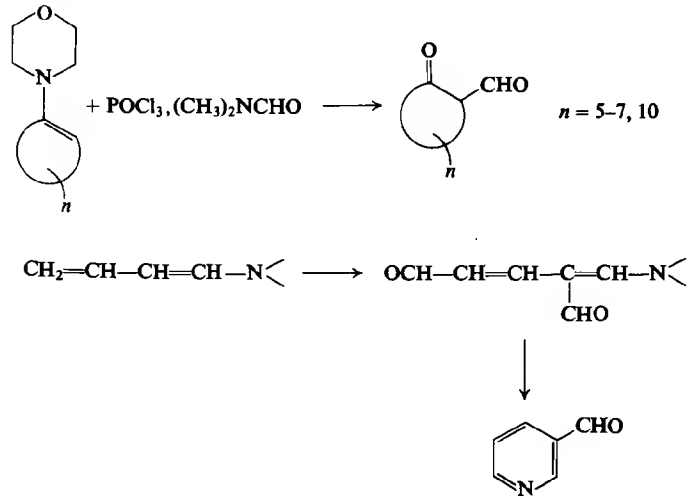




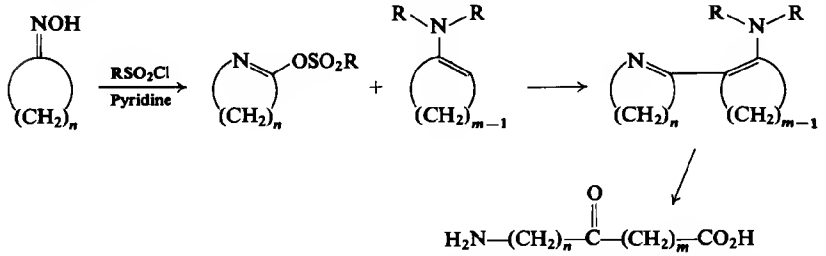
An interesting rearrangement which is based on the intramolecular acylation of an enamine by an ester is found in the aromatization of the adduct derived from N-methylpyrrole and an acetylenedicarboxylic ester (*407,408*).



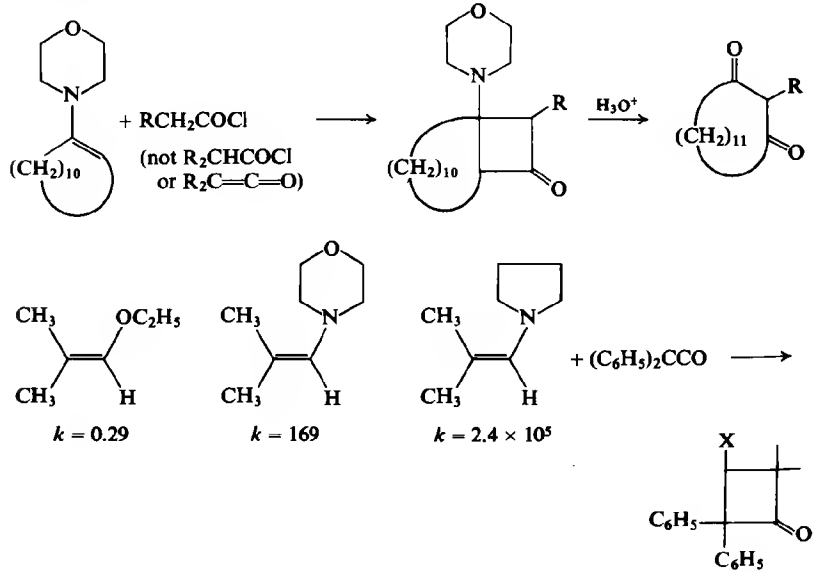
Enamine acylations have been extended to include the Vilsmeier reaction (*409*) and thus provide a method for the generation of formyl ketones without the use of strong base. By this method an unsaturated potential trialdehyde could be formed as an intermediate in a pyridine-3-carboxaldehyde synthesis (*410*).

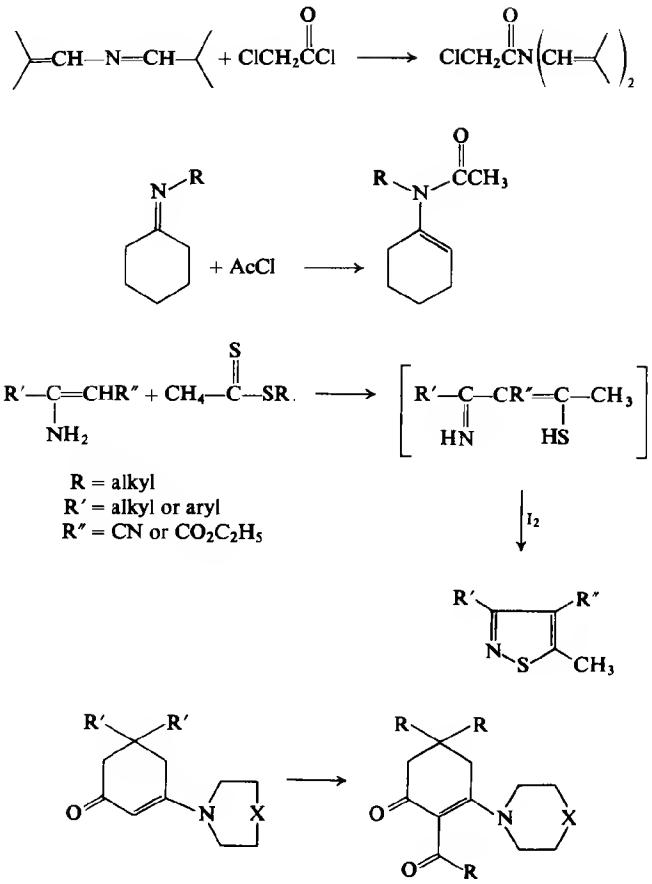


Closely related is the reaction of enamines with O-sulfonyl lactams (*411–413*), which has extended the versatility of Hünig's carboxylic acid extension sequence to compounds with a terminal amine function.



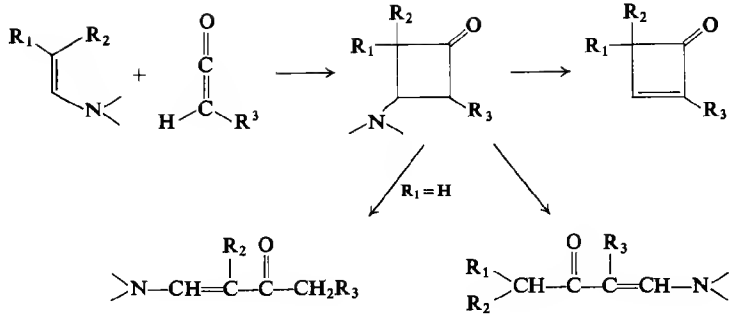
The acylation of enamines derived from cyclic ketones, which can lead to the acyl ketone or ring expansion (*692–694*), was studied by NMR and mass spectroscopic analysis of the products (*695,696*). In a comparative study of the rates of diphenylketene addition to olefins, a pronounced activation was observed in enamines (*697*). Enamine N- and C-acylation products were obtained from reactions of Schiff's bases (*698*), vinylogous urethanes (*699*), cyanamides (*699*), amides (*670,700*), and 2-benzylidene-3-methylbenzothiazoline (*672*) with acid chlorides, anhydrides, and dithioesters (*699*).

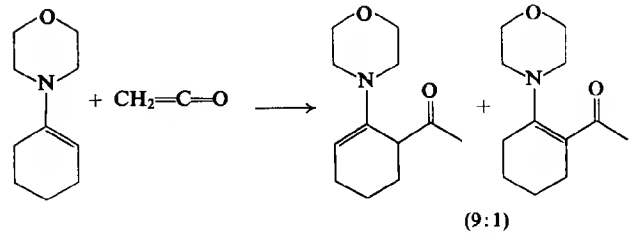




VIII. Reactions with Ketenes

The intermediacy of ketenes in some enamine acylation reactions using acid chlorides was described above (*386,387*). Direct addition of ketene to enamines was studied simultaneously by several groups (*414–420*). The initially formed aminocyclobutanone products could be isolated in some instances, depending on the substitution of the initial enamine. Opening to give either the acylated enamine or the alternative vinylogous amide was found to occur spontaneously or on heating, particularly in adducts derived from enamines with an olefinic proton.





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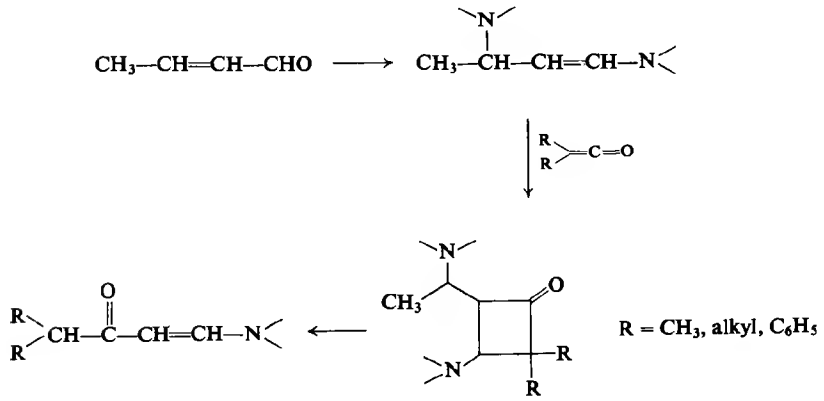
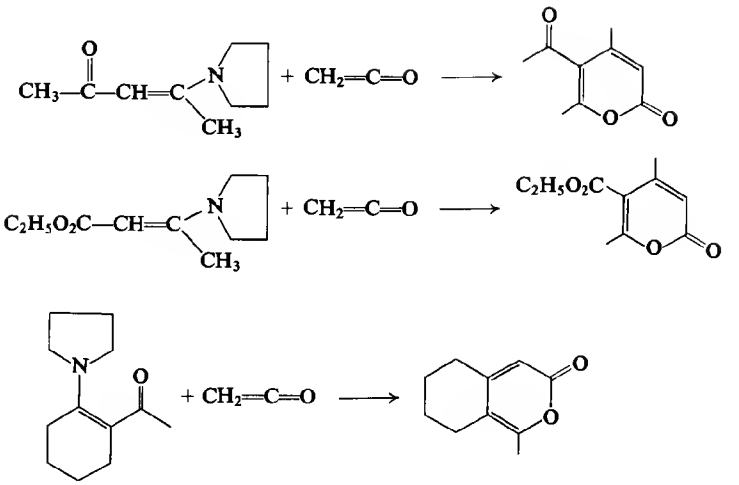
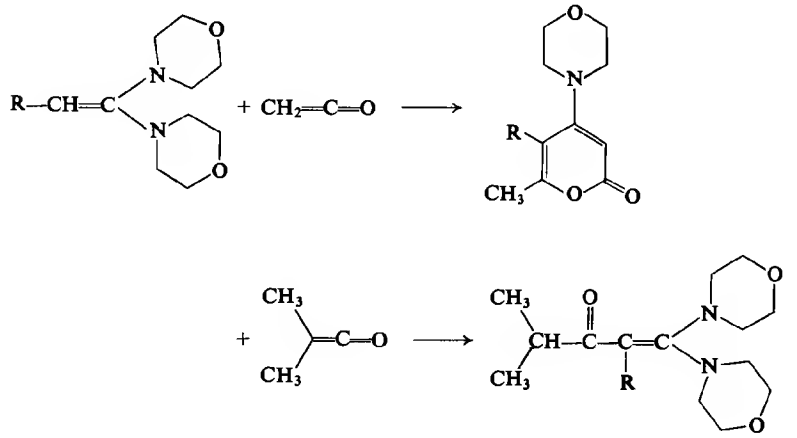


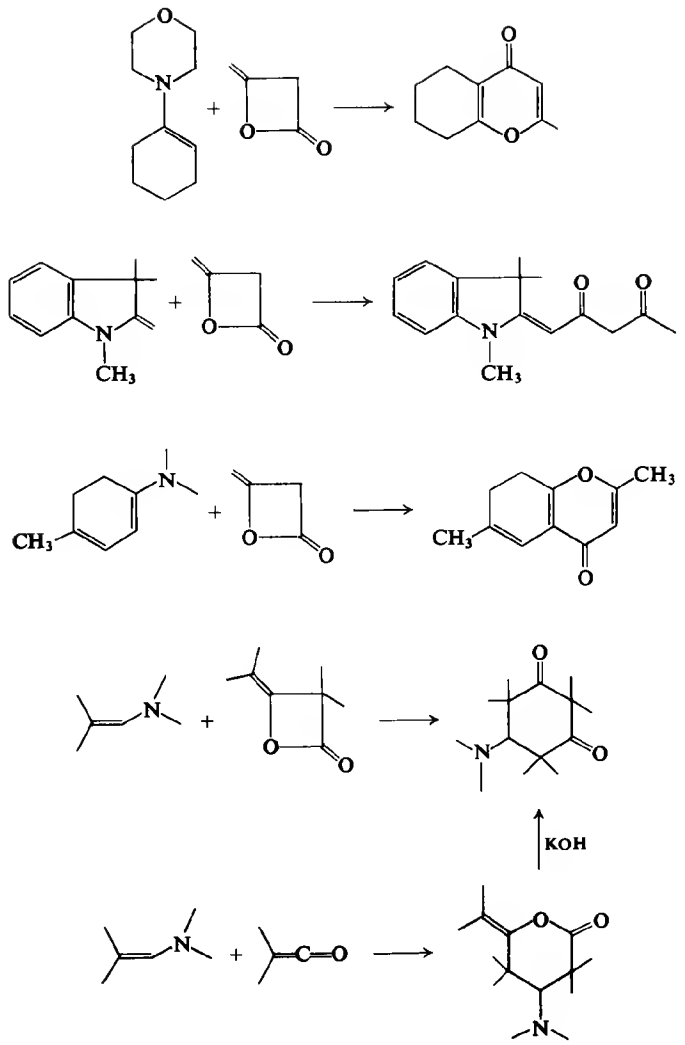
The reactions of vinylogous amides and vinylogous urethanes with excess ketene were found to give α-pyrones (*421*), which could also be obtained from further reactions of acylated enamines with ketene (*383,421*).



Analogously, the reactions of ketene aminals with ketene or dimethyl ketene gave γ-amino-α-pyrones and the linear acylation products, respectively (*422*).



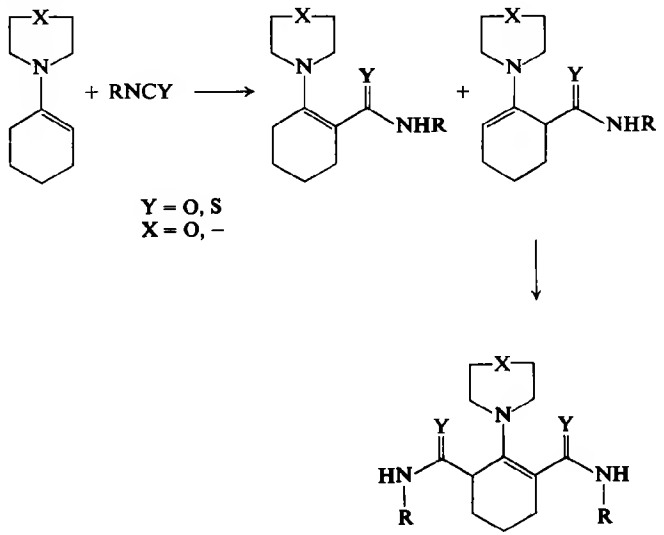
On the other hand γ-pyrones or 1,3-diketones could be obtained from the reactions of ketone derived enamines with diketene (*423–426*). The addition of dimethyl ketene dimer to aldehyde or ketone derived enamines produced cyclohexanediones (*425,426*).



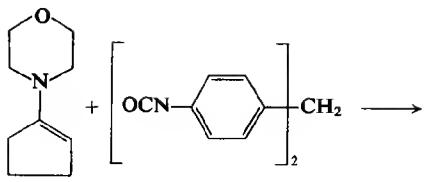
IX. Reactions with Isocyanates

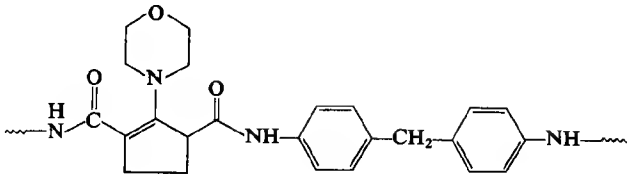
The addition of phenylisocyanate (*427*) to enamines was soon found to lead to double acylation products. In the case of the cyclohexanone derived enamine, the first proposal (*428*) of a second acylation on nitrogen was

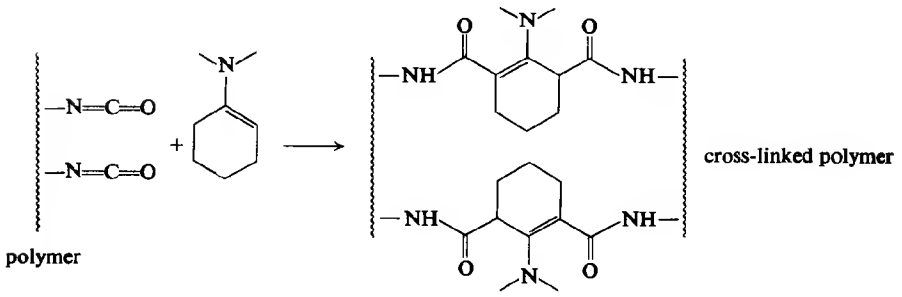
revised in favor of the α,α′-carbon diacylation product (*383,427,429–432*). The vinylogous urea, thiourea, or vinylogous amide structures, expected from reactions of enamines with isocyanates, isothiocyanates, and acid chlorides, are often minor acylation products (*383,429*). Generation of α-substituted, α′-directed enamines then gives rise to α,α′-disubstituted products. The preferred loss of the α′ proton in α-acylated zwitterionic intermediates is a consequence of stereoelectronic control in the initial acylation, which produces an equatorial α proton from cyclohexanone derived enamines, in which the carbon–hydrogen bond has poor overlap potential with respect to the adjacent carbonyl and imonium functions. However, the choice of protons to be lost is also a function of the stability of the imonium function. Thus the more stable pyrrolidine derived imonium intermediates show a larger amount of vinylogous amide formation than the more reactive intermediates in which the imonium group is part of a six-membered ring. Benzoyl and arylsulfonylisocyanates reacted with enamines at greater rates (*433*).



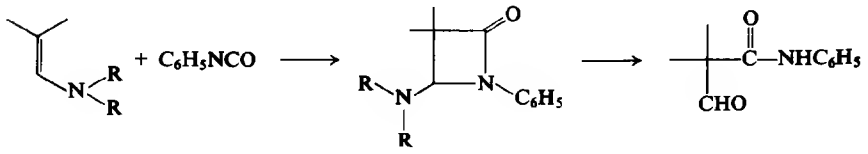
The facile α,α′ diacylation with arylisocyanates has been applied to the synthesis of polymers (*434–436*), while the monoacylation products have been used as intermediates for the synthesis of substituted α-quinolones and their sulfur analogs (*437*).

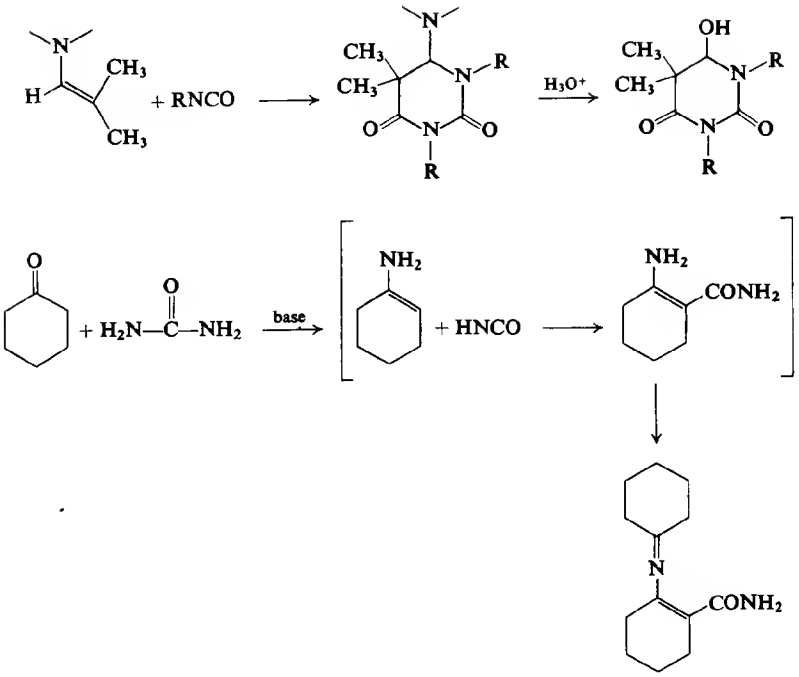




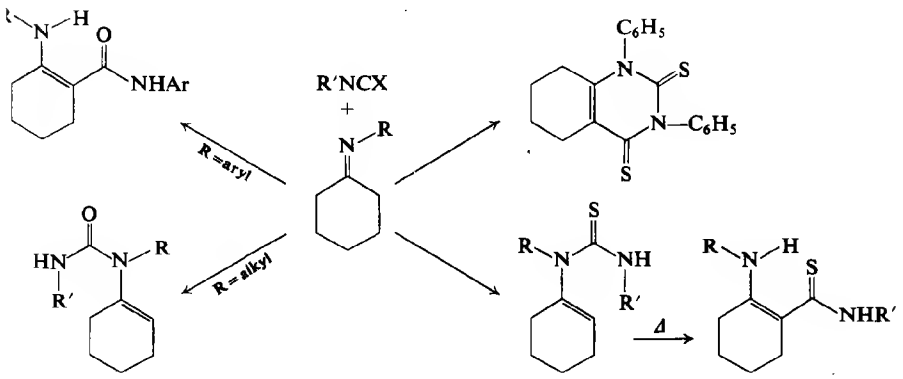


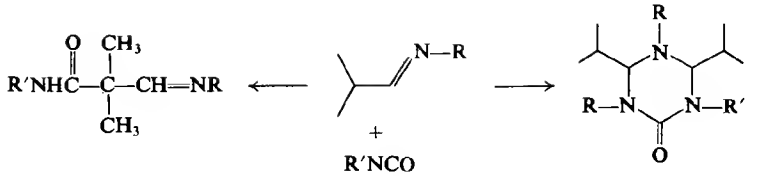
The addition of phenylisocyanate to aldehyde-derived enamines resulted in the formation of aminobutyrolactams (*438,439*). As aminal derivatives these products can be hydrolyzed to the linear aldehyde amides and thus furnish a route to derivatives of the synthetically valuable malonaldehyde–acid system. With this class of reactions, a second acylation on nitrogen becomes possible and the six-membered cyclization products have been reported (*440*). Closely related to the reactions of enamines with isocyanates is the condensation of cyclohexanone with urea in base (*441*).





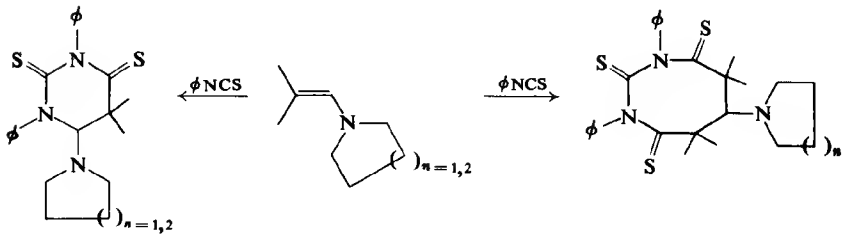
Schiff's bases also underwent C or N acylation with isocyanates (*698*) and isothiocyanates (*698,701*). Further studies provided 2:1 and 2:2 reaction products of arylisothiocyanates and enamines (*702*) and polymers derived from enamines and bisisocyanates (*703*).

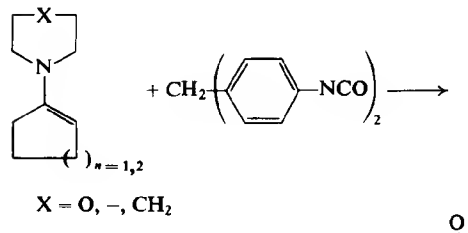




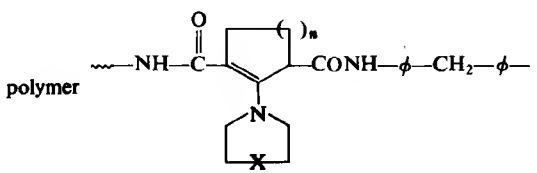
R = isopropyl, *t*-butyl

R = methyl, ethyl





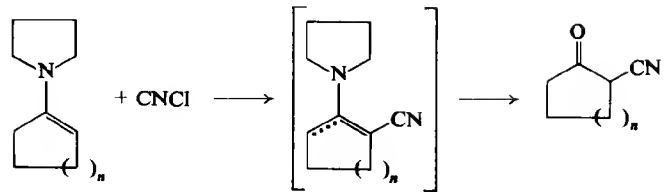
X = O, –, CH_2



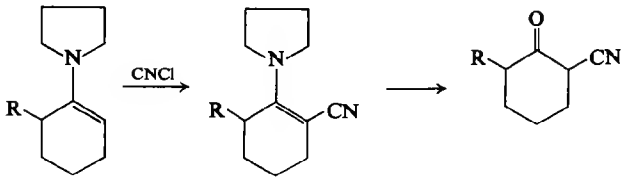
polymer

X. Cyanolation of Enamines

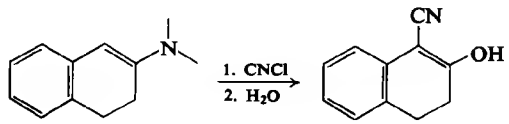
The introduction of nitrile groups alpha to ketone functions by the reactions of enamines with cyanogen chloride (*9,442,443*) provides a convenient alternative to the chlorination and cyanide displacement sequence or the scheme of formylation, isoxazole generation, and subsequent cleavage of the heterocycle to an α-cyano ketone. The use of aryl cyanates (*444,445*) may prove to be a further improvement in the synthesis of α-cyano ketones. Cyanogen bromide and cyanogen iodide, however, lead to halogenation of enamines (*442,443*).

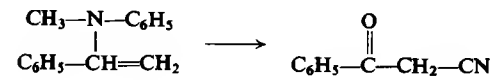


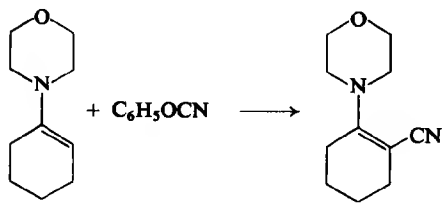
n = 1–5

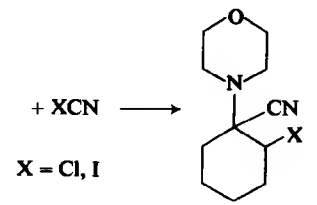


R = CH_3, C_6H_5





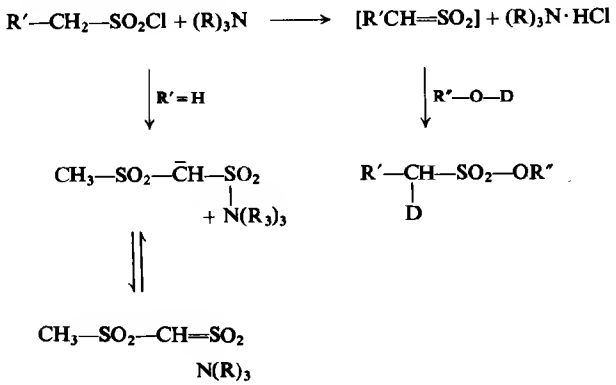




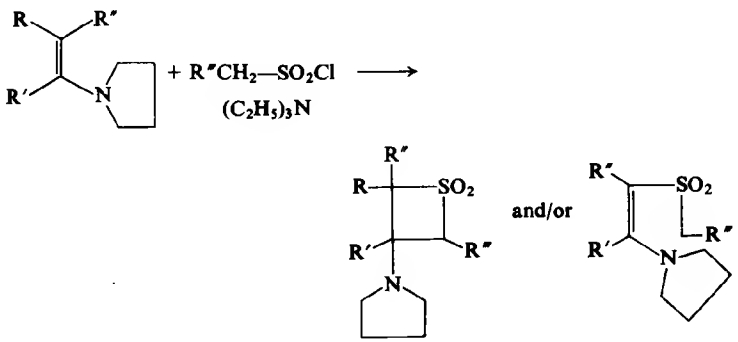
X = Cl, I

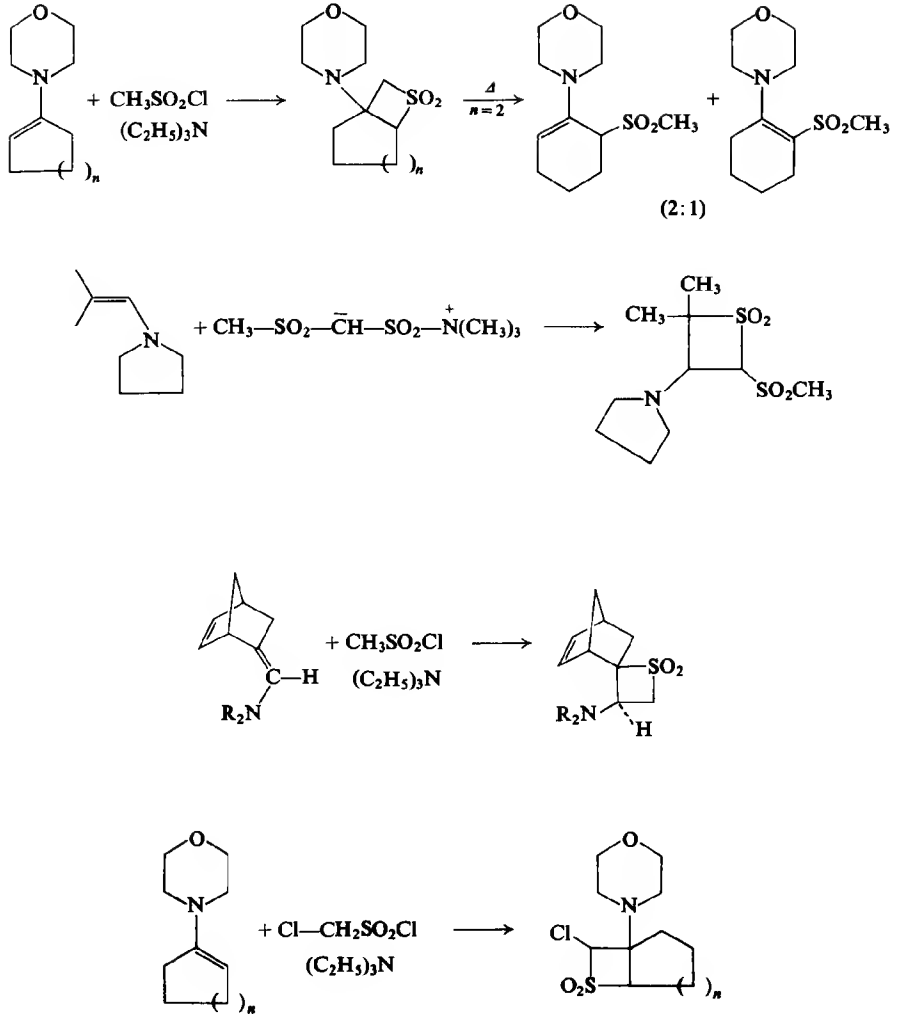
XI. Reactions with Sulfonyl Chlorides, Sulfinyl Chlorides, and Sulfenyl Chlorides

Aliphatic sulfonyl chlorides that have α-hydrogen substituents, react with simple tertiary amines, such as trimethylamine, to generate sulfenes or perhaps their amine adducts (*446*). These species are suggested by the incorporation of one (but not more) deuterium atoms on reaction of sulfonyl chlorides with deuterated alcohols and triethylamine (*447–450*). A 2:1 adduct of sulfene and trimethylamine with proposed sulfonyl–sulfene structure could be isolated (*451*).

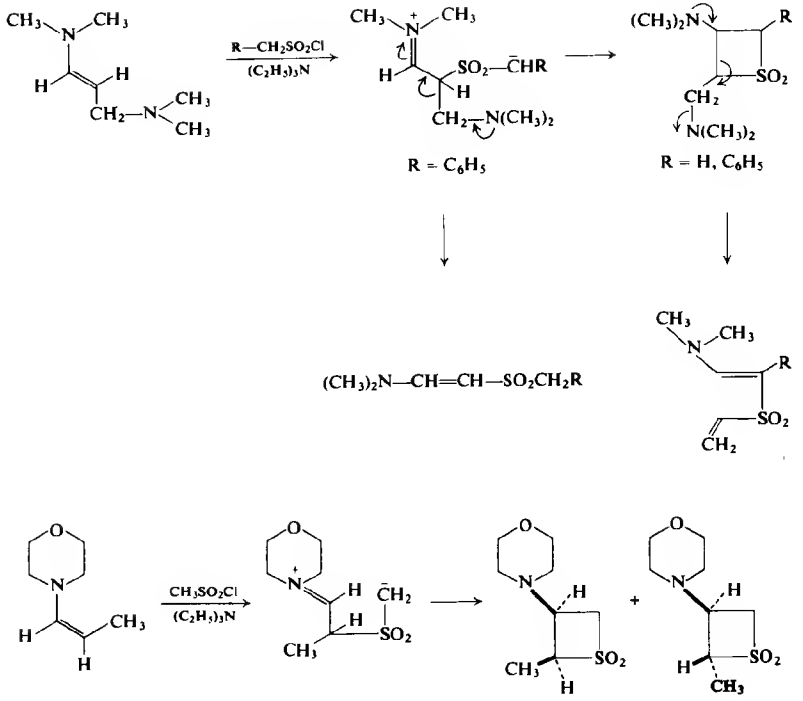


The condensation of sulfonyl chlorides with enamines (*452,453*) derived from aldehydes and ketones has led to four-membered-ring sulfones, presumably through such intermediates (*454–464*). Open sulfonation products have also been obtained, particularly from ketone-derived enamines and from α-disubstituted sulfonyl chlorides.

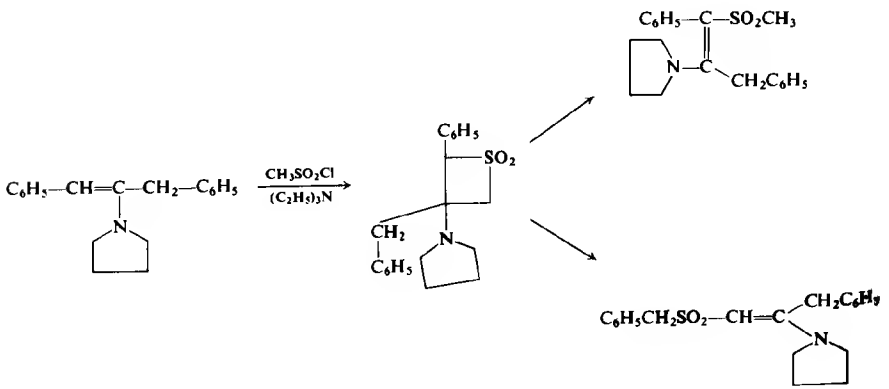




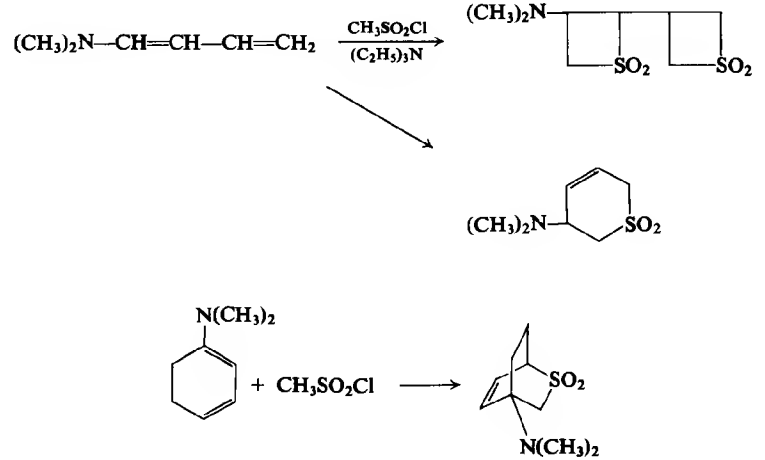
The intermediacy of zwitterionic species was proposed for the addition of phenylsulfenyl chloride to dimethylaminomethyl-substituted enamines (*465,466*). They receive support from the observed lack of stereospecific addition of methylsulfonyl chloride to *cis*-morpholinopropene (although the *trans* enamine gives only one adduct) (*466*).



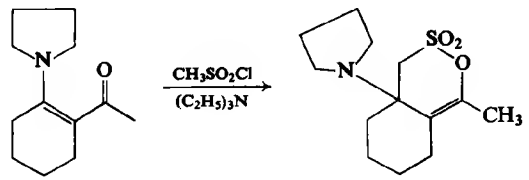
Thermal opening of the cycloaddition products leads to acyclic sulfones (*464,467*).



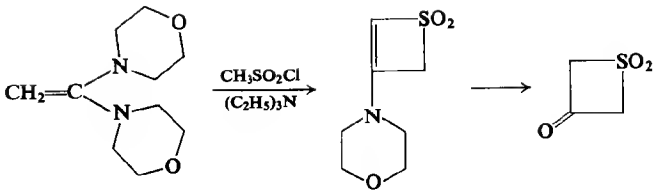
Conjugated dienamines were found to give predominantly double four-membered-ring adducts as well as a small amount of the six-membered-ring adduct (*466,468*). This important result indicates preferred attack at the terminal carbon of the dienamine system (in contrast to alkylation, for instance) in the generation of an initial zwitterionic intermediate. Addition of sulfonyl chloride and triethylamine to a homocyclic dienamine gave only the bridged product (*446*).

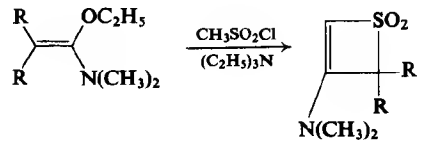


Reactions of vinylogous amides with methanesulfonyl chloride also led to the formation of six-membered rings. Here the initial attack on oxygen produces a zwitterionic intermediate which can collapse to an enol sulfonic acid lactone (*383,469*).

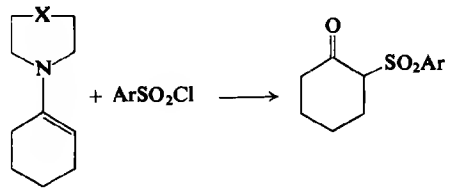


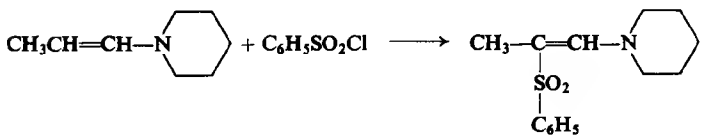
The formation of four-membered-ring sulfones and α-sulfonyl amides has also been applied to the reaction of methanesulfonyl chloride with ketene aminals and acetals (*470–473*).



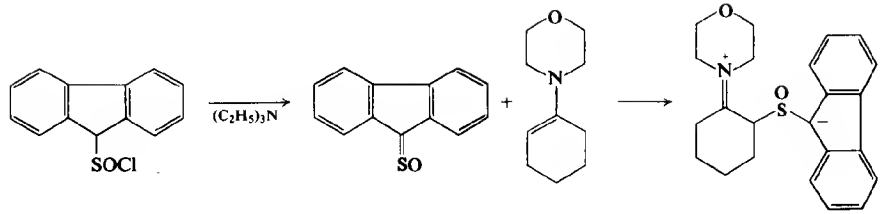


Arylsulfonyl chlorides and enamines reacted to give sulfonated enamines (*452,453,474*). The latter could be hydrolyzed to the corresponding sulfonyl ketones.

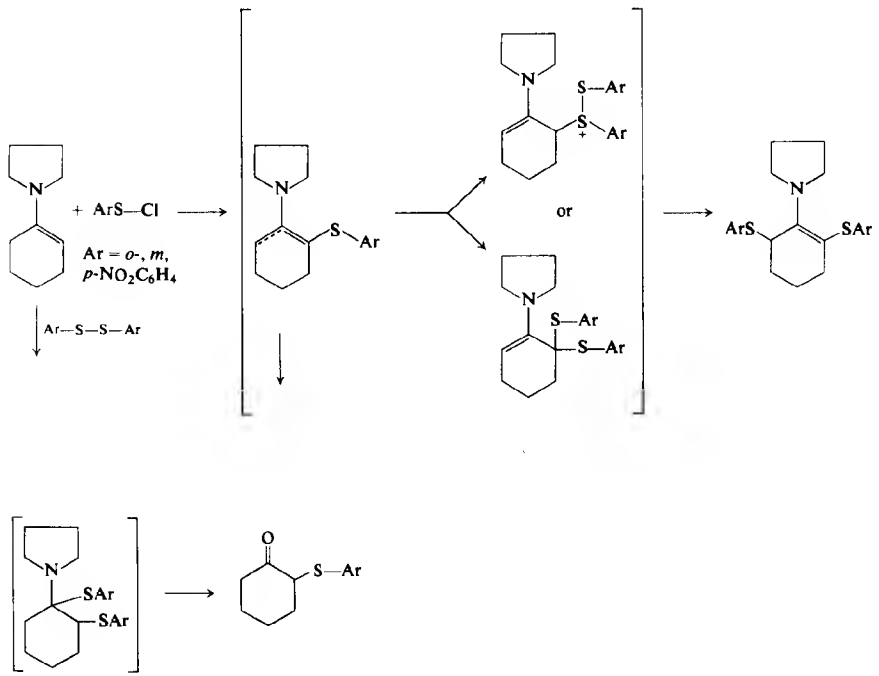




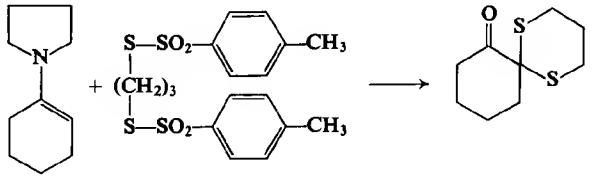
Hydrogen chloride has also been eliminated from sulfinyl chlorides by addition of triethylamine. The thioketone oxide obtained from 9-fluorenesulfinyl chloride reacted with morpholinocyclohexene to give a zwitterionic adduct (*475*).



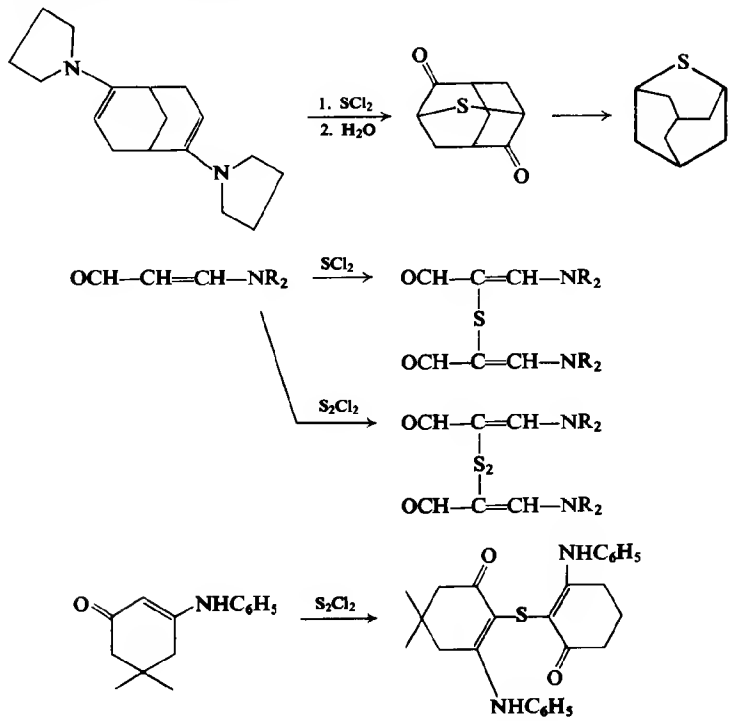
In the reactions of arylsulfenyl chlorides with enamines one encounters an unusual result for enamine chemistry, in that the formation of 2,6-disubstituted cyclohexanone enamines predominates over the formation of monosubstitution products (*474*). A rationalization of this result suggests the formation of an intermediate which can act as an intramolecular electrophile in formation of the second carbon–sulfur bond.

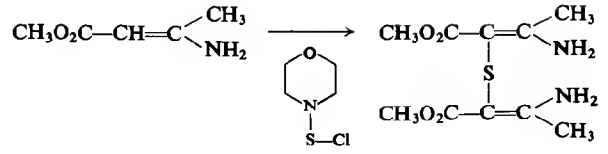


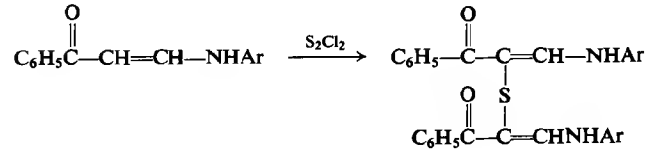
The double α substitution of enamines with propane-1,3-dithiol ditosylate has provided a route for the introduction of a thioketal, which has found use as a blocking group in modified steroid (*476*) and terpene (*477*) syntheses.

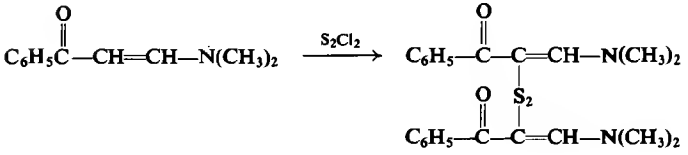


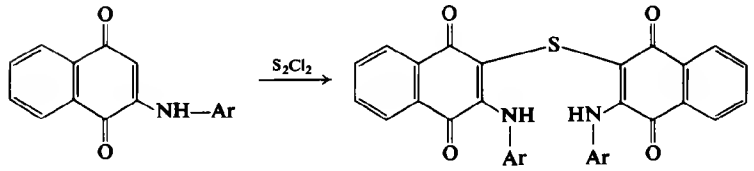
An interesting bridged-sulfur compound, which is a natural constituent of Iranian oil, has been synthesized (*478*) by the reaction of a bicyclic bis-enamine with sulfur dichloride and subsequent Wolff–Kishner reduction of an initial sulfur-bridged diketone. Sulfur dichloride has also been added to a number of vinylogous amides (*479*).

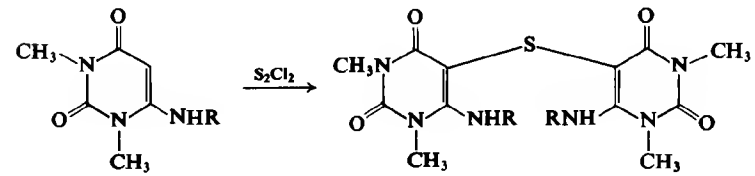




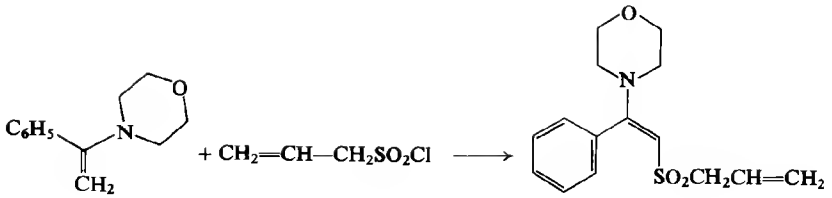


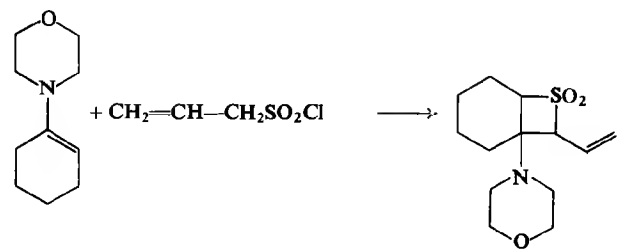


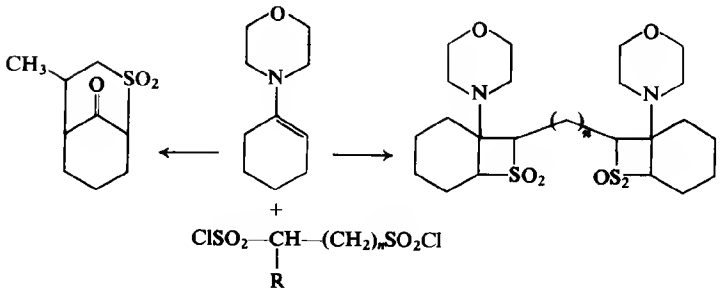




Allylsulfonyl chloride and enamines furnished the sulfonyl enamines or cyclic sulfones (*704*), and alkyldisulfonyl chlorides gave 1:2 adducts or bicyclic products with morpholinocyclohexene.

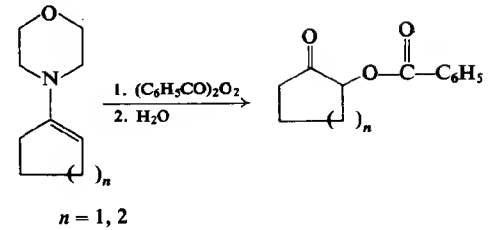


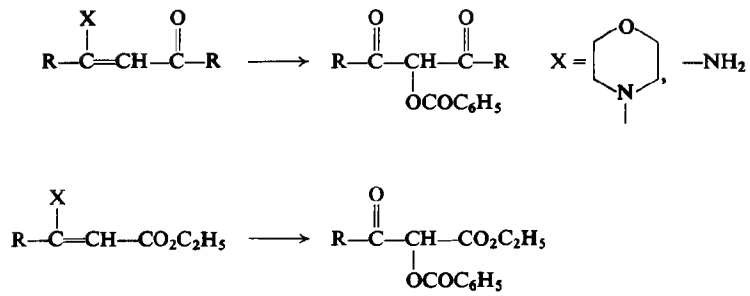


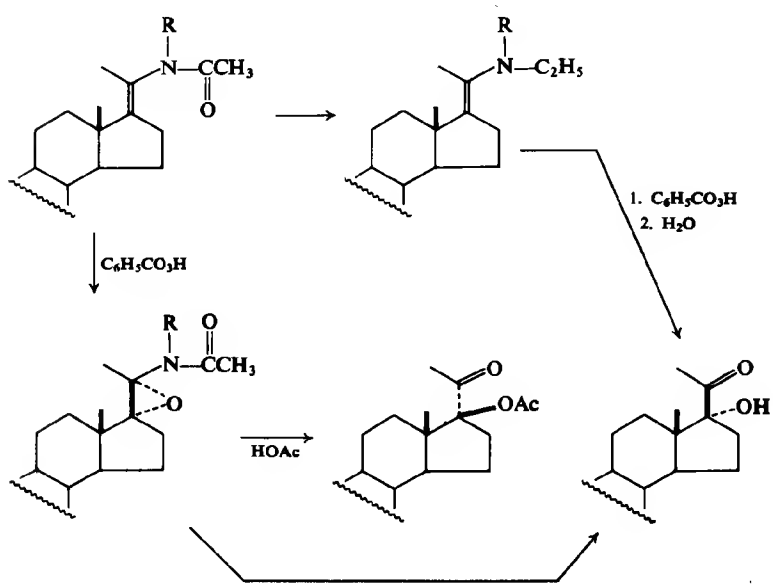


XII. Oxygenation of Enamines

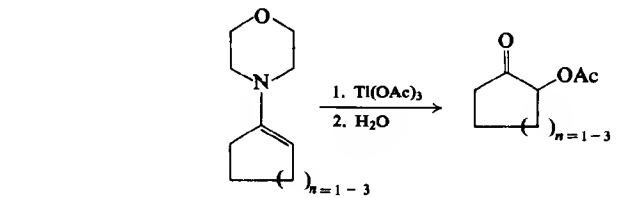
Reactions of benzoylperoxide with morpholinocyclohexene and morpholinocyclopentene furnished the corresponding α-benzoyloxyketones in modest yields (*480,481*). This oxidation has also been applied to some vinylogous amides (*482*), and the expected faster rate of reaction of the enamine system as compared with enamides has been noted in derivatives of 20-ketosteroids, in reactions with perbenzoic acid (*59,483*).

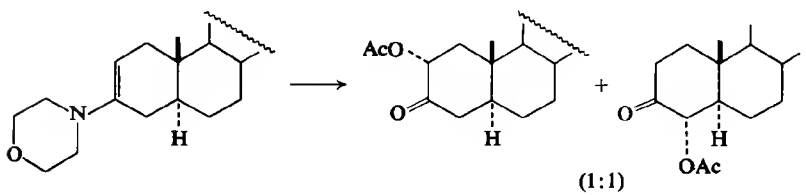


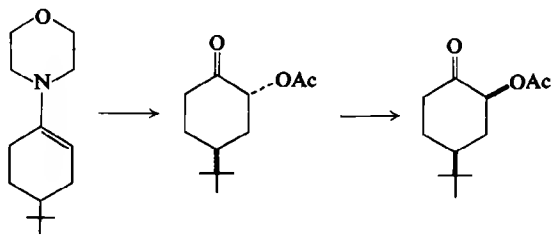


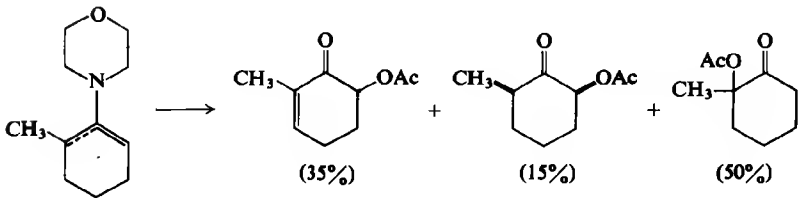


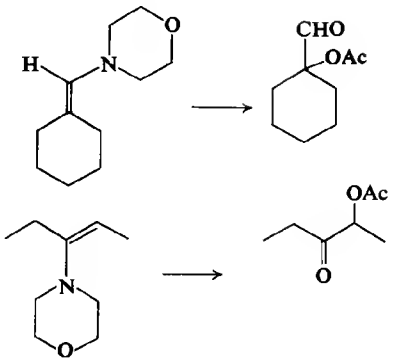
The formation of α-acetoxyketones by oxidation of enamines with thallic acetate has been studied in detail (*21*) and found to be of preparative value (80% yields) particularly in five- and six-membered-ring ketone derivatives. Enamines of linear or seven-membered-ring ketones were oxidized also, but at very much slower rates. Enamines of aldehydes with α-hydrogen substituents underwent self-condensations during the oxidation reactions. Lead tetraacetate was less satisfactory as an oxidizing agent.



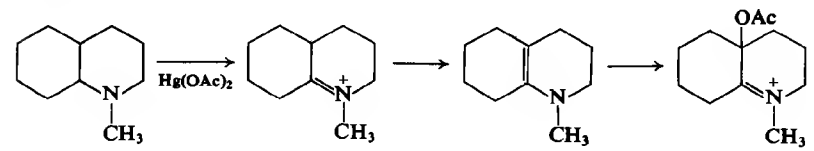




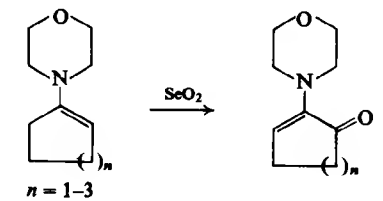




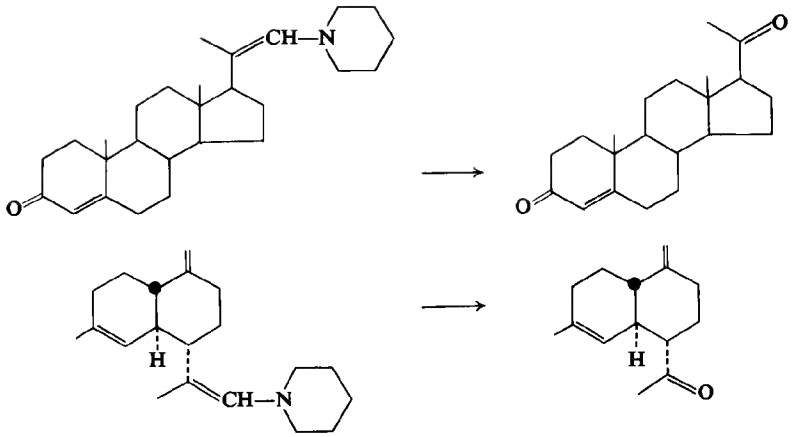
While the oxidation of tertiary amines has been used extensively for the generation of enamines, an example of overoxidation with formation of an acetoxyimonium salt has been reported (*484*).



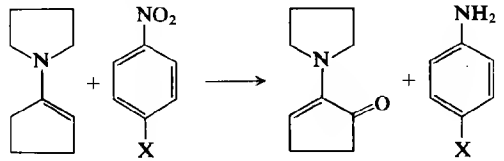
Reactions of enamines with selenium dioxide gave low yields of enamino ketones (*38*). Aromatization of cyclohexanone derived enamines could be largely prevented by the use of acetonitrile as solvent for the reaction. Even then, yields were considerably below the limit of 50%, imposed by the generation of an equivalent of water.



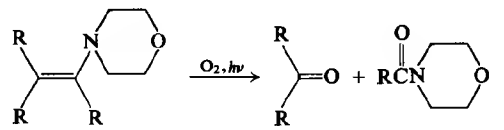
Oxidative degradations of aldehyde derived enamines with ozone (*4*) or sodium dichromate (*485–487*) have been applied to the formation of progesterone from 3-ketobisnor-4-cholenaldehyde.



From the oxidation of enamines with aromatic nitro compounds α-keto-enamines were obtained in modest yields (*705*). Photooxygenation led to cleavage of the enamine double bond (*706,707*).

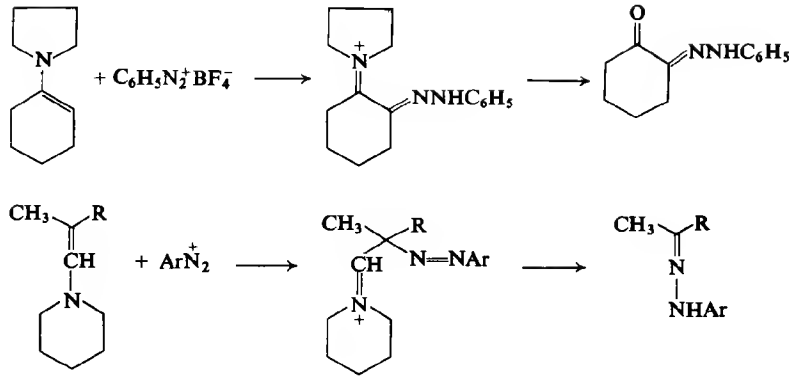


X = $CO_2C_2H_5$, $COCH_3$, OCH_3



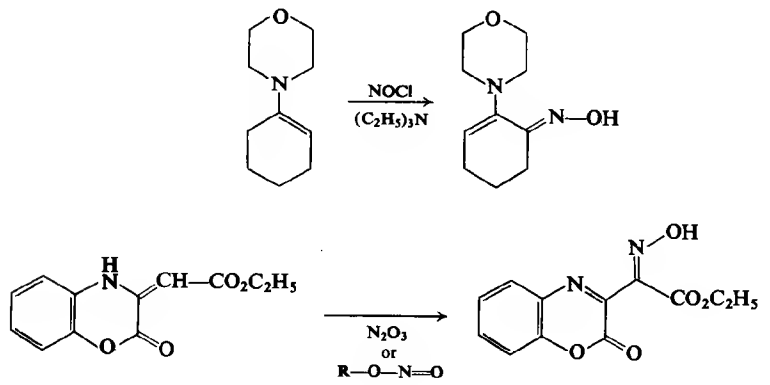
XIII. Formation of Enaminohydrazones and Oximes

The coupling of enamines with aromatic diazonium salts has been used for the syntheses of monoarylhydrazones of α-diketones (*370,488–492*) and α-ketoaldehydes (*488,493*). Cleavage of the initial enamine double bond and formation of the phenylhydrazone of acetone and acetophenone has been reported with the enamines of isobutyraldehyde and 2-phenylpropionaldehyde. Rearrangement of the initial coupling product to the hydrazone tautomer is not possible in these examples.



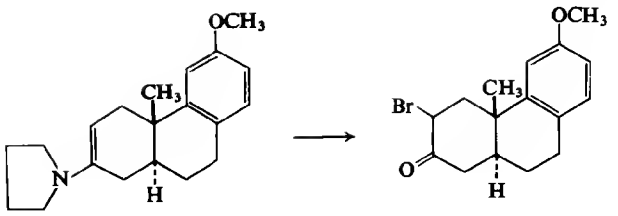
R = CH_3, C_6H_5

An α-oximino enamine was formed by the reaction of nitrosyl chloride and triethylamine with morpholinocyclohexene (*494*). Oxime functions have also been introduced into carbonyl conjugated enamines with isoamyl nitrite or N_2O_3 (*495*).

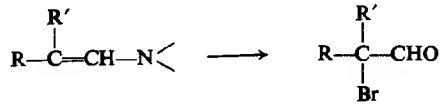


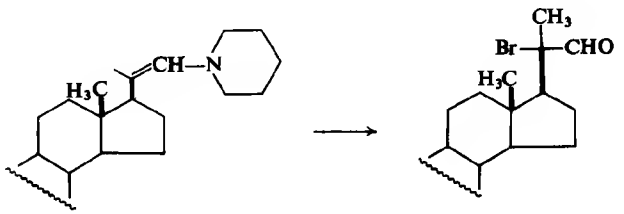
XIV. Halogenation of Enamines

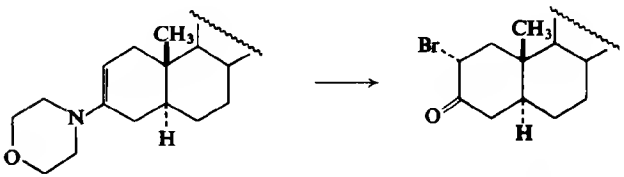
The selective bromination of a ketone in the presence of another susceptible functional group was achieved in a diterpene synthesis (*240*). A competing bromination of an anisole ring could be avoided here through the use of a pyrrolidine enamine derivative for activation of the methylene group adjacent to the carbonyl function.



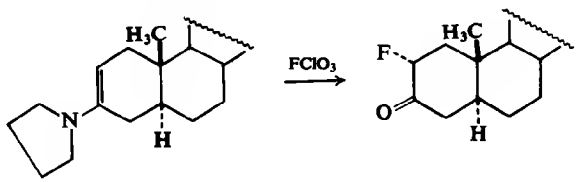
The reaction has also been applied to the syntheses of a number of α-bromoaldehydes (*497,498*) and 2-α-bromocholestanone (*21*).

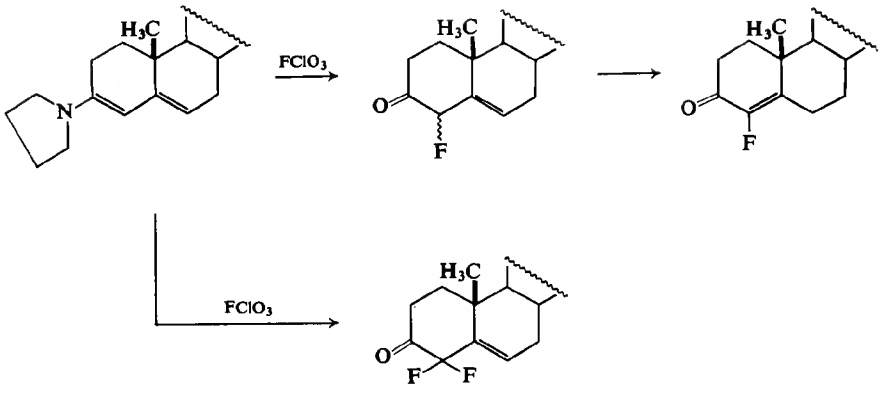


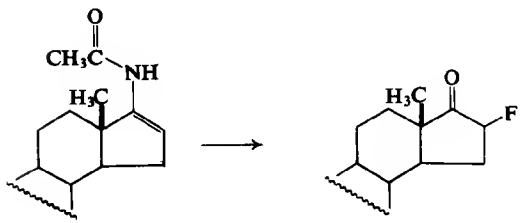




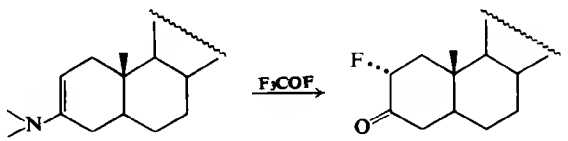
The most extensive use of enamine halogenations has, however, been in the attachment of fluorine to the steroid skeleton (*499–503*). The formation of a 16-fluoro-17-ketosteroid by the reaction of perchlorofluoride with a 17-enamide has also been reported (*504*).

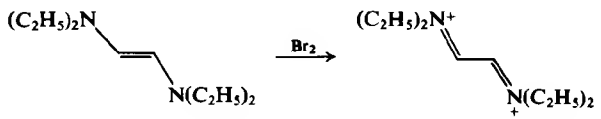






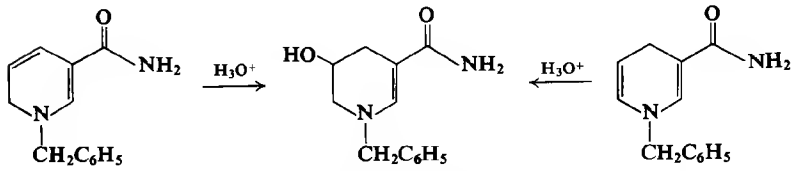
Fluorination of an enamine, enol ether, or enol acetate with CF_3OF gave 60–70% yields of fluoroketone (*708*). Bromination of an endiamine gave the bis-imonium salt (*647*).





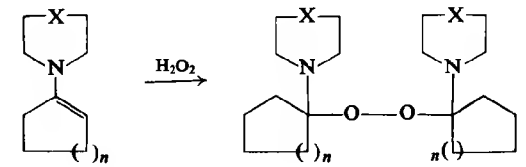
XV. Miscellaneous Addition Reactions

While the usual consequence of hydration of enamines is cleavage to a secondary amine and an aldehyde or ketone, numerous cases of stable carbinolamines are known (*102*), particularly in examples derived from cyclic enamines. The selective terminal hydration (*505*) of a cross-conjugated dienamine–vinylogous amide is an interesting example which gives an indication of the increased stabilization of the vinylogous amide as compared to simple enamines, which is also seen in the decreased nucleophilicity of the conjugated amino olefin–carbonyl system.



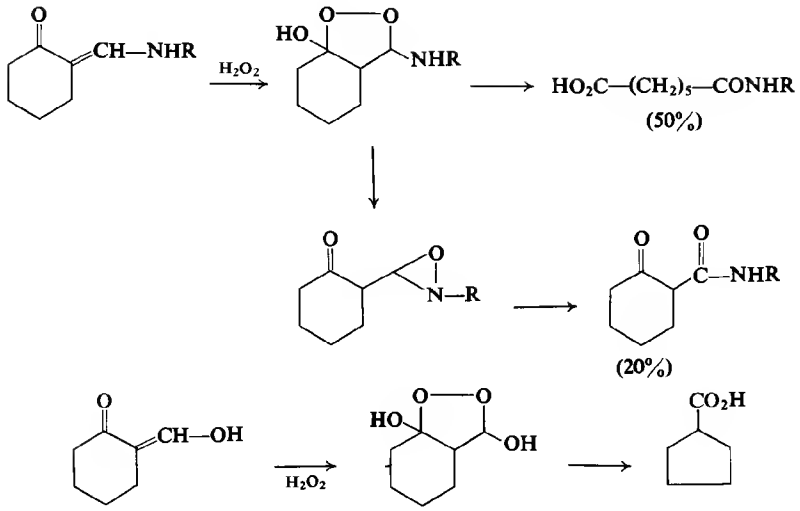
(claimed, but perhaps 4-OH compound)

Extension of the hydration reaction to hydrogen peroxide has shown that stable peroxides are formed from enamines and the imonium salts derived from secondary amines and ketones (*506,507*).

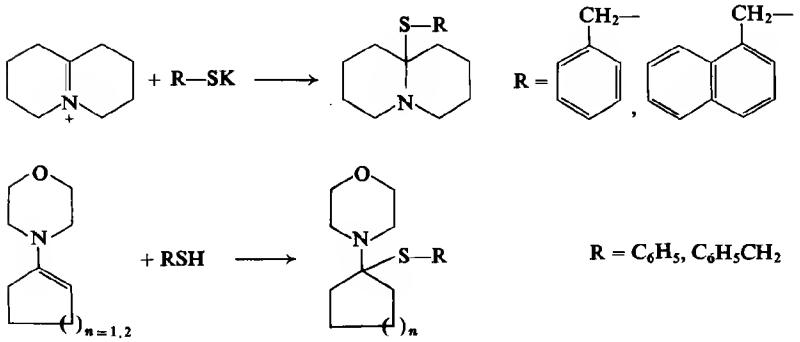


X = O, CH_2

The application of this addition to aminomethylene ketones provides a convenient synthesis of monoamides of pimelic acid (*508*). It should be noted that the corresponding oxidation of hydroxymethylene cyclohexanone leads to ring contraction and formation of cyclopentanoic acid.

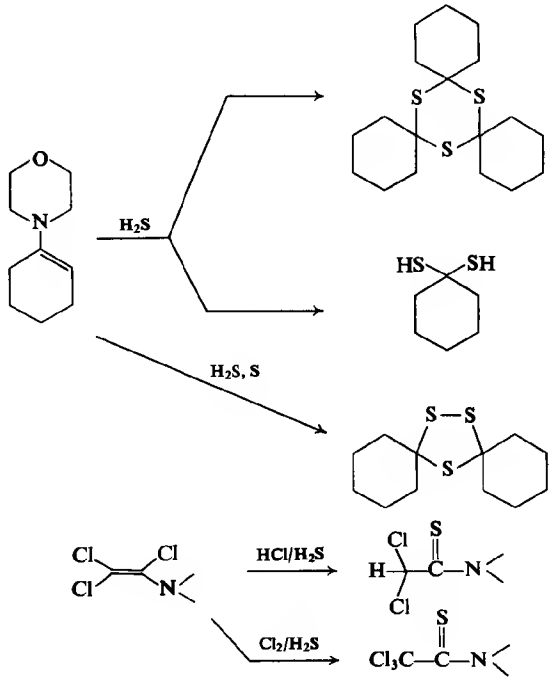


While carboxylate anions do not add to the imonium function of ketone derived enamines, such as morpholinocyclohexene, when these are combined with carboxylic acids (*38*), the addition of thiophenol or benzyl mercaptan leads to α-aminothioethers (*509,510*).

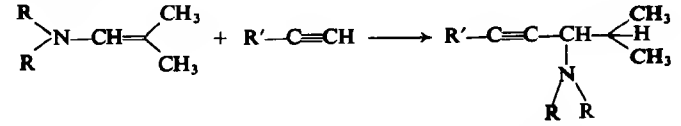


Addition of hydrogen sulfide results in formation of monomeric gem dithiols or trimeric thioketals (*511,512*). The initially reported thione formation (*513–515*), analogous to hydration of morpholinocyclohexene

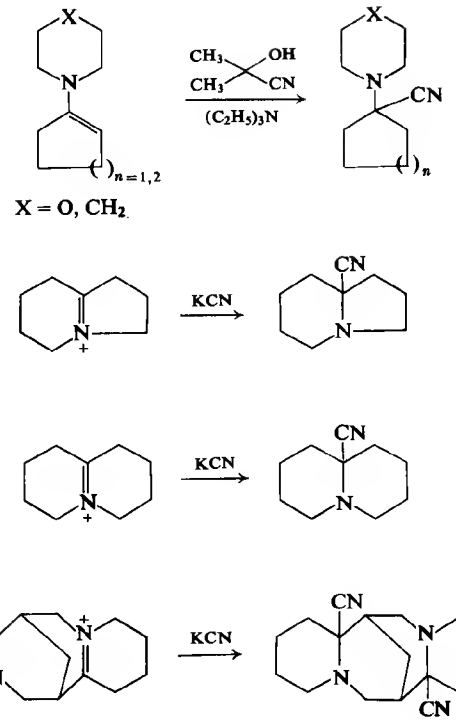
or morpholinocyclopentene, has been discredited (*511,512*). A reaction of the hydrogen sulfide adduct of morpholinocyclohexene with sulfur leads to the interesting sulfur analog of the ozonide structure (*516*). Closely related are the conversions of α-chloroenamines to thioamides (*517*).

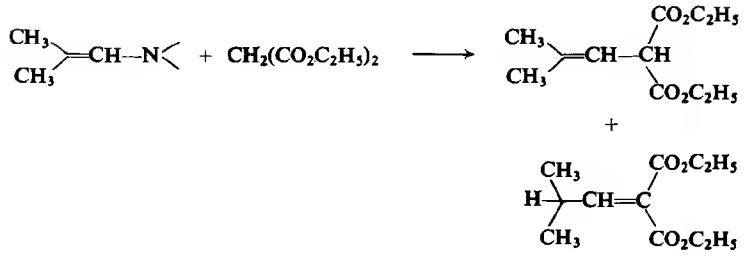


The formation of adducts of enamines with acidic carbon compounds has been achieved with acetylenes (*518*) and hydrogen cyanide (*509,519,520*) (used as the acetone cyanohydrin). In these reactions an initial imonium salt formation can be assumed. The addition of malonic ester to an enamine furnishes the condensation product, also obtained from the parent ketone (*350,521*).

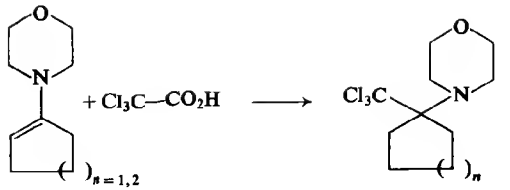


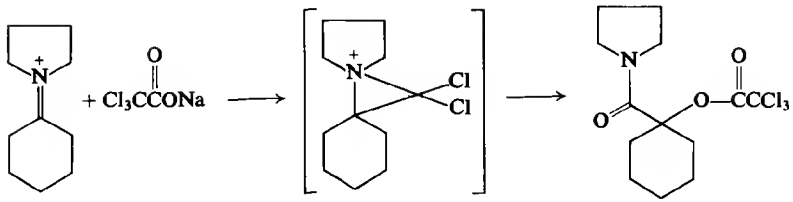
R = CH_3,—$(CH_2)_5$— R′= H, alkyl, C_6H_5, CO_2-alkyl



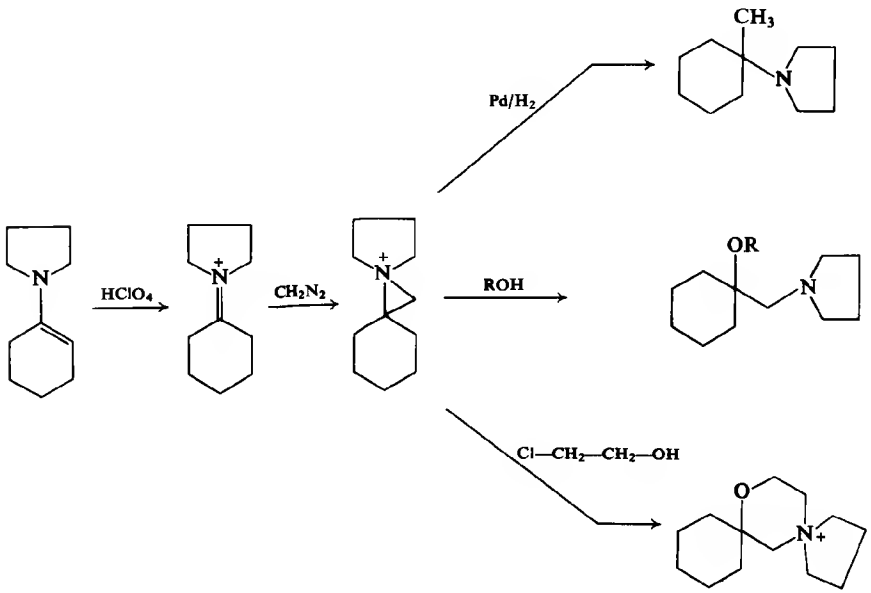


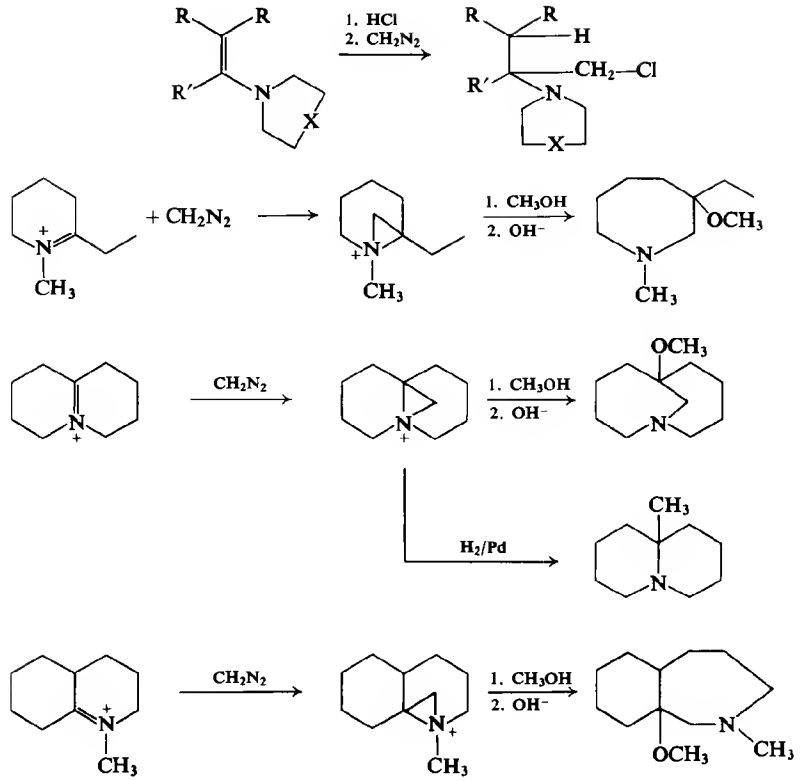
Similarly, α-trichloromethylamines (*522*) were obtained by decomposition of trichloroacetic acid in morpholine enamines, but an amide ester was formed from sodium trichloroacetate and the imonium salt of pyrrolidinocyclohexene (*523*). The product is presumably derived from opening of an intermediate dichloroaziridinium salt.



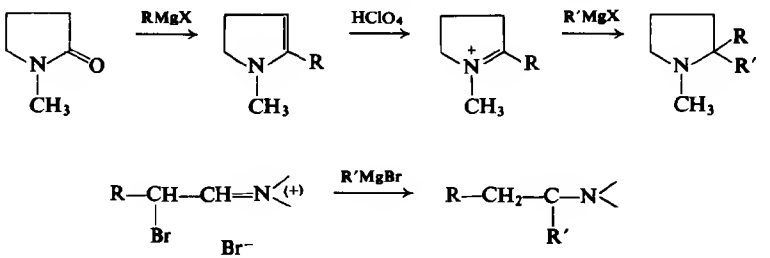


A more general access to the synthetic potential of aziridinium salts is found in the reactions of imonium salts with diazomethane (*225,524,525, 536*).

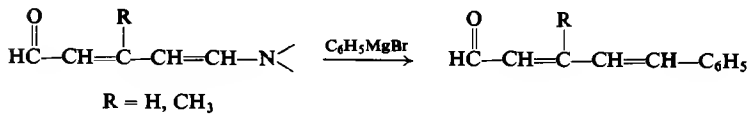




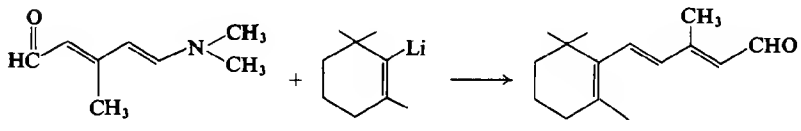
Grignard reagents do not add directly to enamines, but their reactions with the corresponding imonium salts readily furnish tertiary amines (*225,526*). The reductive removal of halogen has been observed in the addition of Grignard reagents to α-bromoimonium salts (*527*).

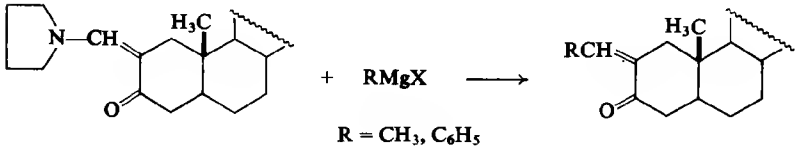


When the enamine is in conjugation with a carbonyl function, as in α-aminomethylene aldehydes (*528,529*), ketones (*530*), or esters (*531*), a Michael addition is found in vinylogous analogy to the reactions of amides. An application to syntheses in the vitamin A series employed a vinyl lithium compound (*532*).

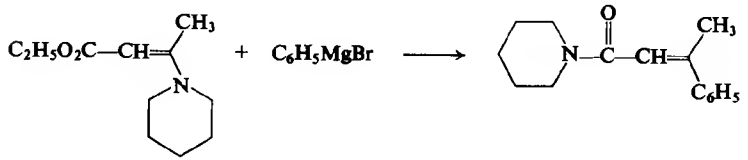


R = H, CH_3

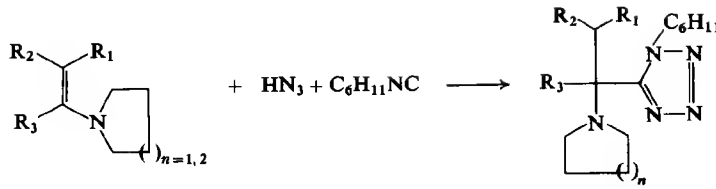


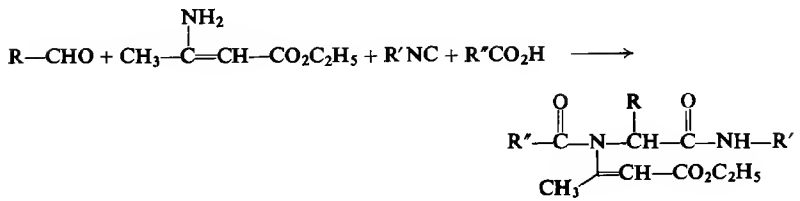


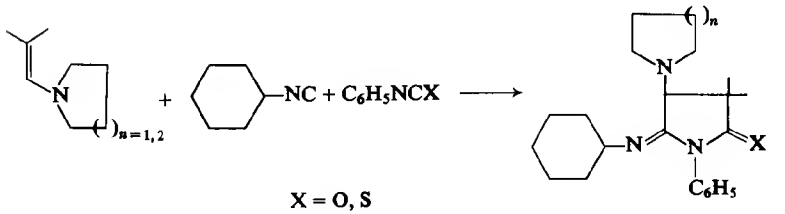
R = CH_3, C_6H_5



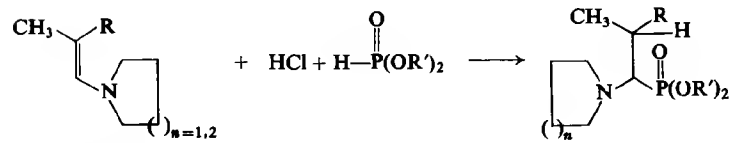
The addition of isocyanides and azide to aldehyde-derived enamines has led to tetrazoles (*533,536*). On the other hand the vinylogous amide of acetoacetic ester and related compounds reacted with aldehydes, isocyanides and acids to give α-acylaminoamides (*534*). Iminopyrrolidones and iminothiopyrrolidones were obtained from the addition of cyclohexylisocyanide and isocyanates or isothiocyanates to enamines (*535*). An interesting method for the formation of organophosphorus compounds is found in the reactions of imonium salts with dialkylphosphites (*536*).





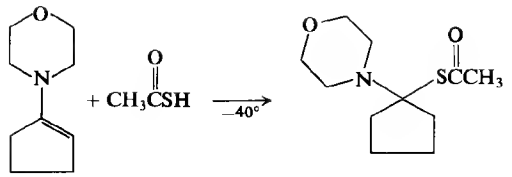


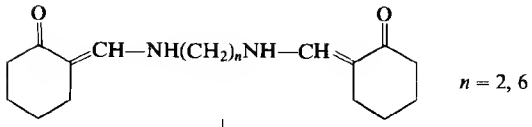
X = O, S

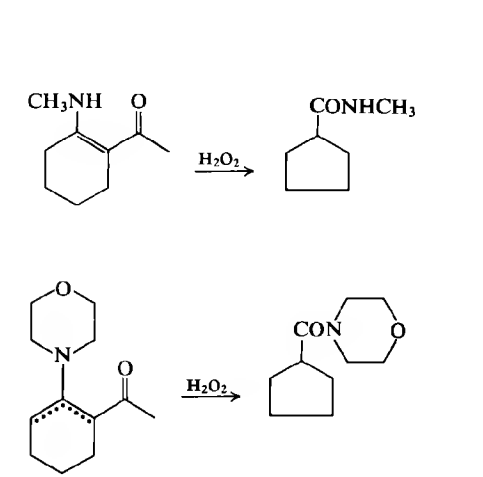


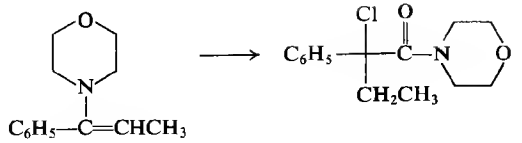
R = H, CH_3
R′ = CH_3, C_2H_5

At low temperature a 1:1 adduct of thioacetic acid and an enamine could be prepared (*709*). The previously described reaction of aminomethylene ketones with hydrogen peroxide was extended to bisaminomethylene compounds. However, acylated cyclohexenamines led to cyclopentanecarboxamides (*710*). Trichloromethyl adducts of enamines and the rearranged amine derivatives were described in a further study (*711*).

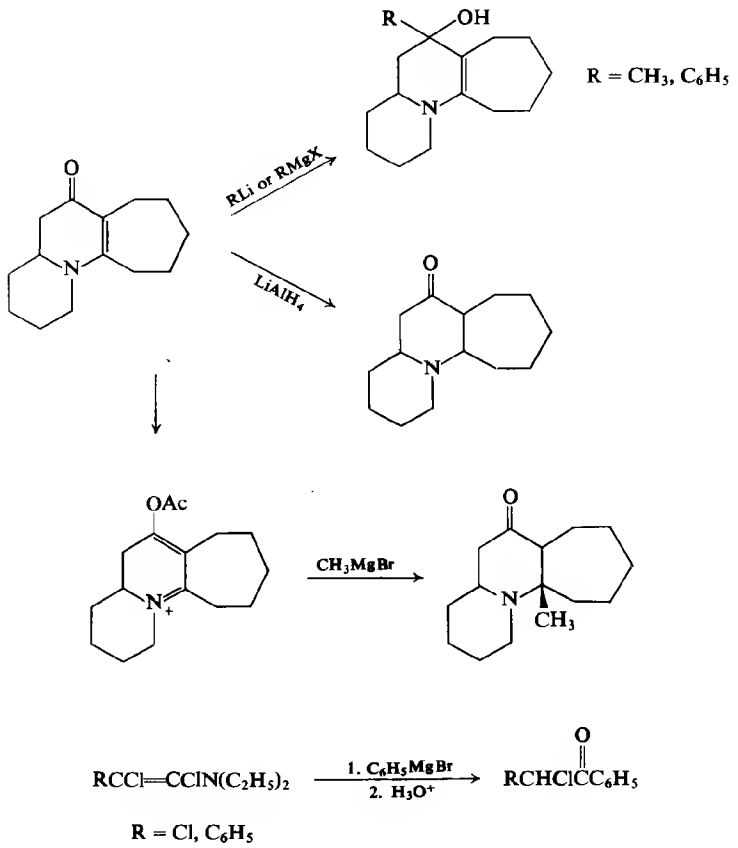






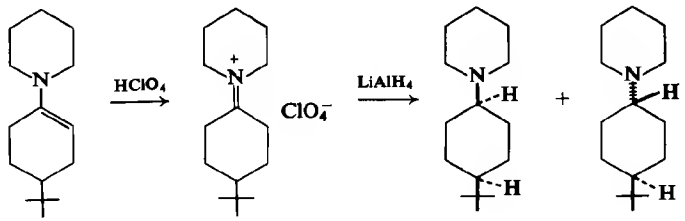


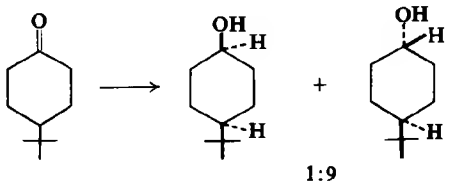
Grignard and alkyl lithium reagents were found to add to the carbonyl group of a tricyclic vinylogous amide. However, the same compound underwent the usual vinylogous reduction with lithium aluminum hydride (*712*). Grignard additions to di- and trichloroenamines gave α-chloro- and dichloroketones (*713*).



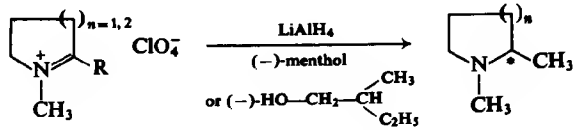
XVI. Reduction of Enamines

The chemical reduction of enamines by hydride again depends upon the prior generation of an imonium salt (*111,225*). Thus an equivalent of acid, such as perchloric acid, must be added to the enamine in reductions with lithium aluminum hydride. Studies of the steric course (*537*) of lithium aluminum hydride reductions of imonium salts indicate less stereoselectivity in comparison with the analogous carbonyl compounds, where an equatorial alcohol usually predominates in the reduction products of six-membered ring ketones.

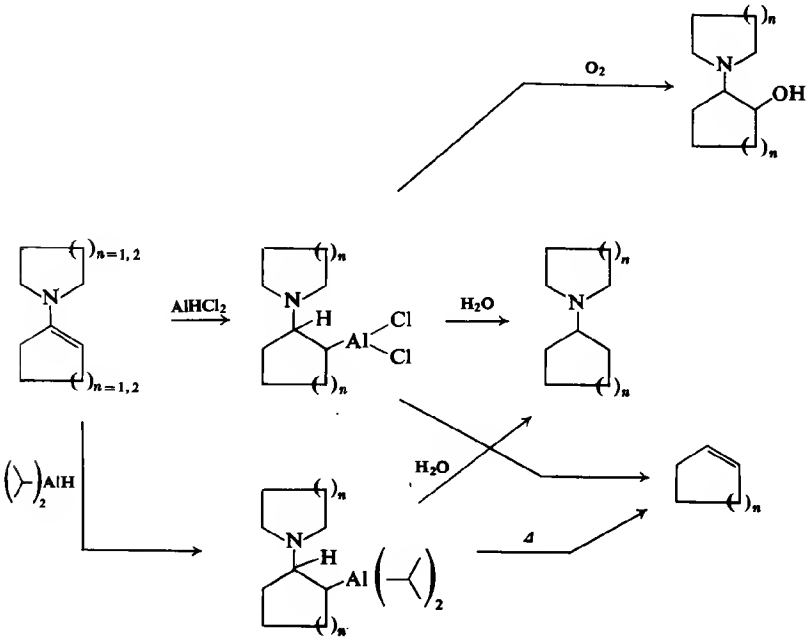




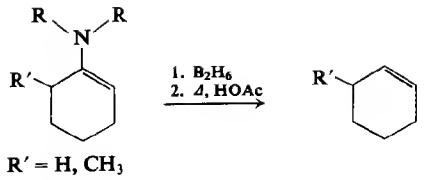
An asymmetric synthesis has used the reduction of imonium salts to optically active tertiary amines with lithium aluminum alkoxy hydrides derived from optically active alcohols (*538,539*).

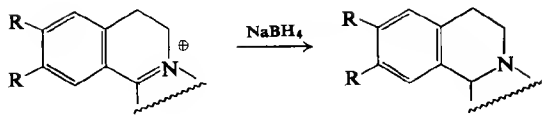


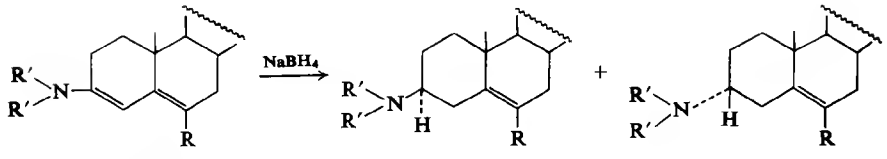
Reactions of enamines with aluminum hydrogen dichloride (*540,541*) ($LiAlH_4$ and $AlCl_3$) or aluminum hydrogen dialkyl compounds (*542*) led to organoaluminum intermediates which could be hydrolyzed to tertiary amines or oxidized to aminoalcohols. The formation of olefins by elimination of the tertiary amine group has also been noted in these reactions.

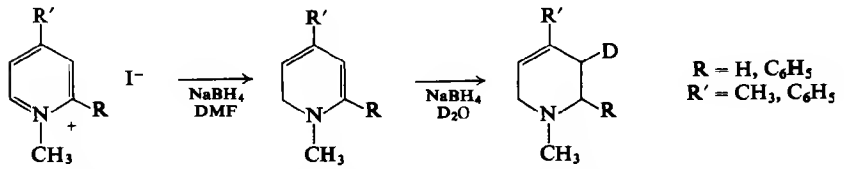


Olefins are also the products of hydroboration of enamines, followed by treatment of the organoborane products with hot acid (*543,544*). The reduction of enamines with sodium borohydride and acetic acid (*545*) and the selective reduction of dienamines with sodium borohydride to give homoallylic tertiary amines (*138–140,225,546,547*), has been applied to the synthesis of conessine (*548*) and other aminosteroid analogs (*545,549–552*). Further examples of the reduction of imonium salts by sodium borohydride can be found in the reduction of Bischler–Napieralski products, and other cyclic imonium salts (*102*).

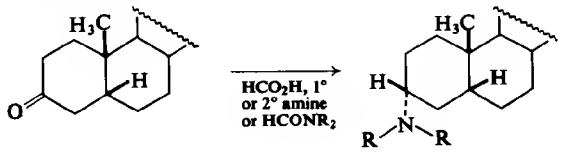


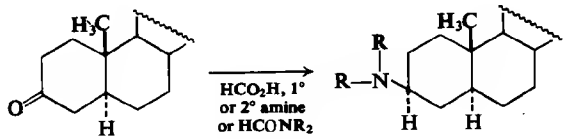


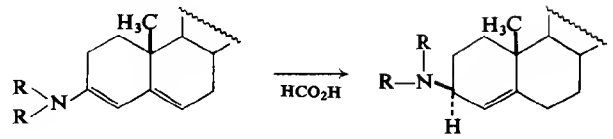


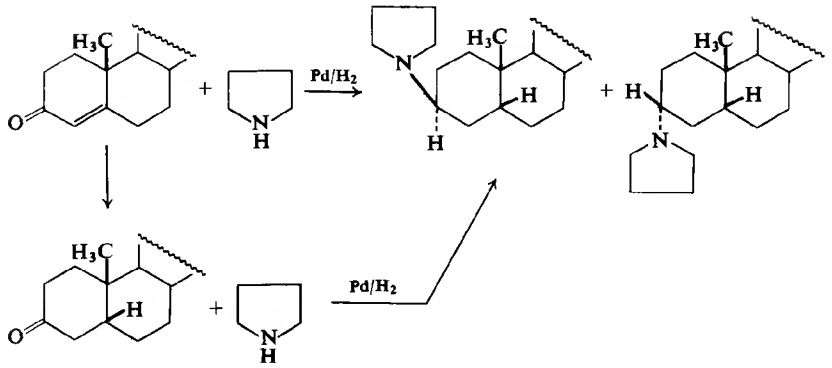


Greater stereoselectivity for the formation of equatorial amines has been found in the reduction of enamines with formic acid or formamides (*553–559*). The selective formation of 3-α-amino-5-β-steroids by this method and of 3-β-amino-5-β-steroids by catalytic reduction (*560*) of the corresponding enamines is of interest.

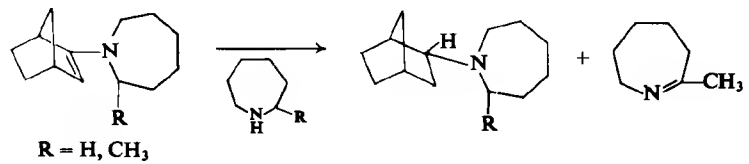




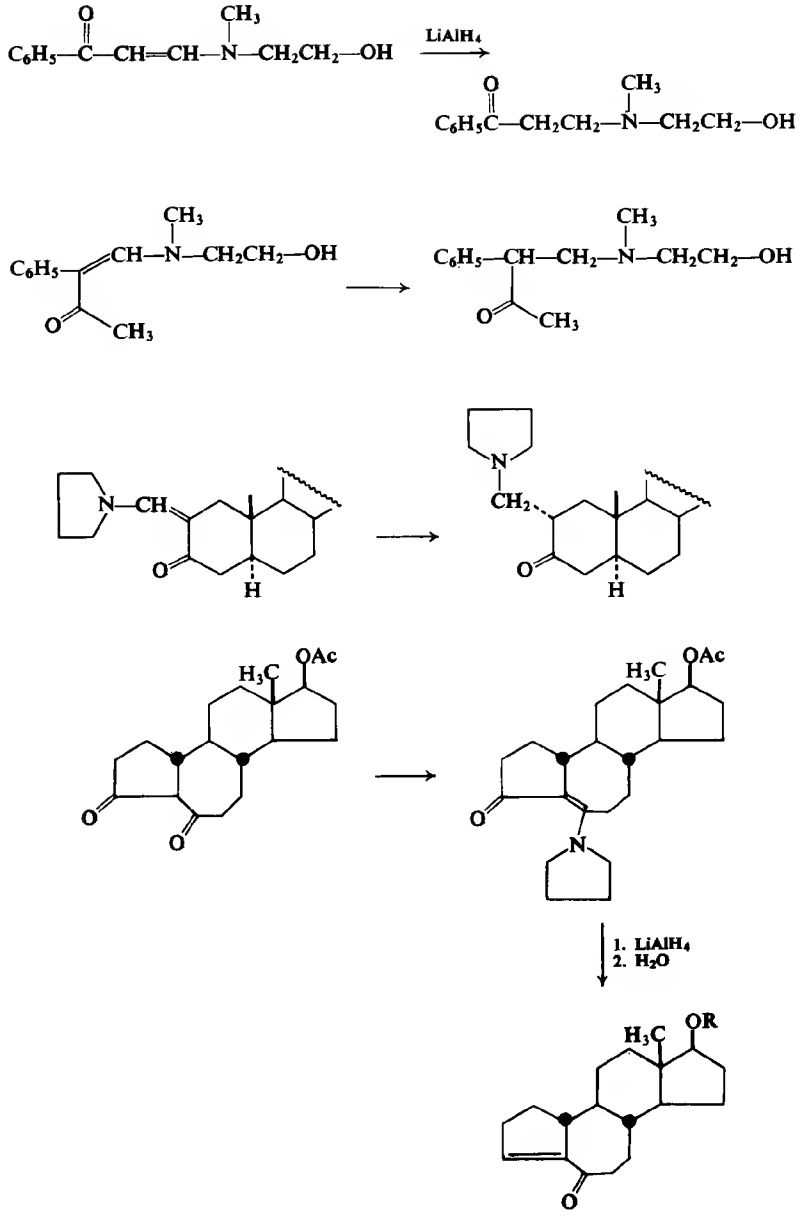




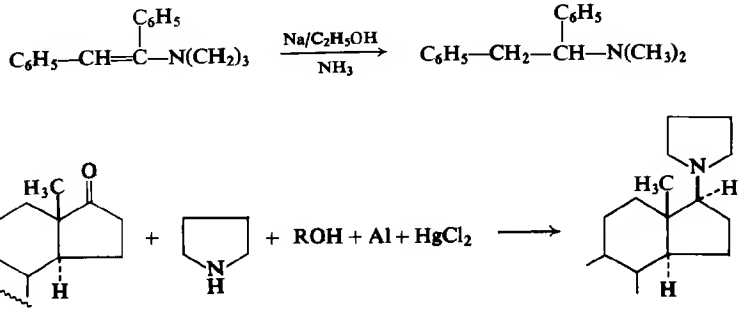
An unexpected reduction of enamines by secondary amines such as pyrrolidine, piperidine, and particularly hexamethyleneimine was discovered in the formation of the norbornanone enamines and extended to hexamethyleneiminocyclopentene (*561,562*).



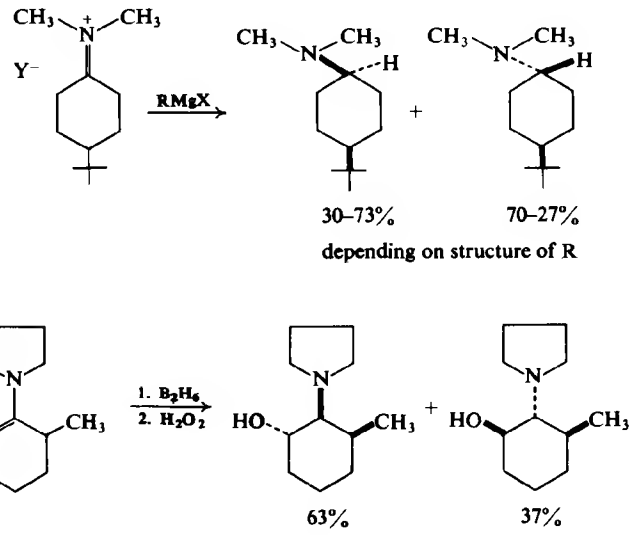
Vinylogous amides undergo reduction with lithium aluminum hydride, by Michael addition of hydride and formation of an enolate, which can resist further reduction. Thus β-aminoketones are usually produced (*309, 563,564*). However, the alternative selective reduction of the carbonyl group has also been claimed (*565*).

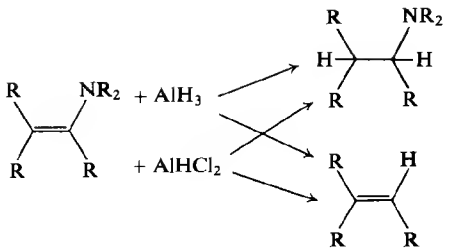


Reduction of the enamine system of an aminostilbene by sodium in liquid ammonia (*189*) and of a 17-enaminosteroid by aluminum and mercuric chloride in alcohol (*560*) have also been reported.



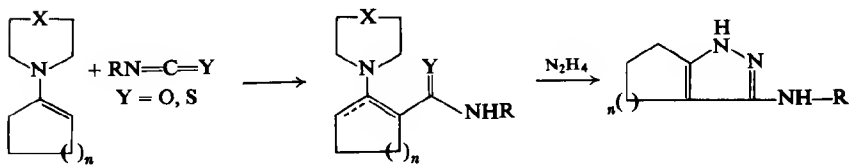
The stereochemical course of reduction of imonium salts by Grignard reagents was found to depend on the structure of the reagent (*714*). Hydroboration of enamines and oxidation with hydrogen peroxide led to amino-alcohols (*715*). While aluminum hydrogen dichloride reacted with enamines to yield mostly saturated amines and some olefins on hydrolysis, aluminum hydride gave predominantly the unsaturated products (*716*).

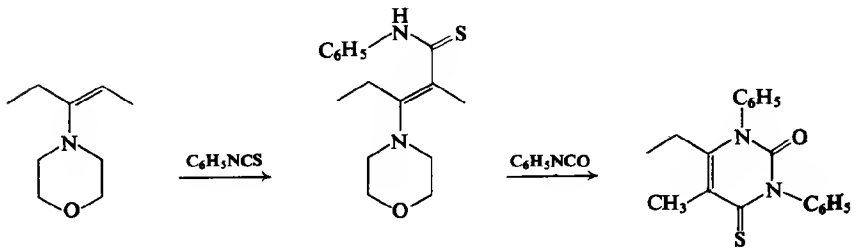




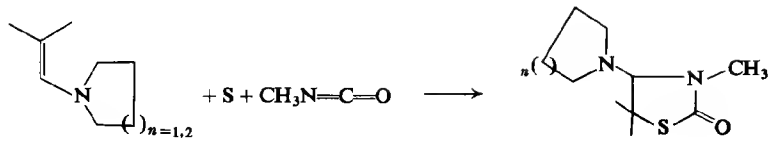
XVII. Use of Enamines in Syntheses of Heterocycles

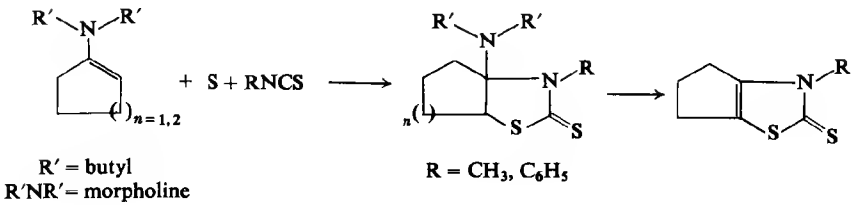
One of the extensively investigated applications of enamines to heterocyclic syntheses is based on the bifunctional character of enamine acylation products. Thus the vinylogous ureas and thioureas obtained from enamines and phenylisocyanate and phenylisothiocyanate (*433*) have been converted to aminopyrazoles and thiouracils with hydrazine (*566*) and phenylisocyanate (*567*).



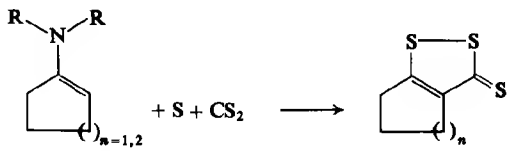


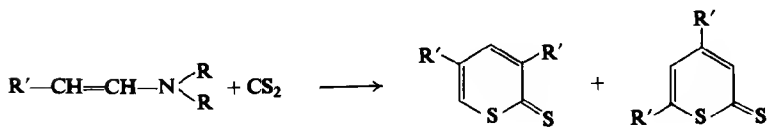
Reactions of enamines with isocyanates (*568*) and isothiocyanates (*569*) in the presence of sulfur gave 1,3-thiazolidine-2-ones and 1,3-thiazolidine-2-thiones.



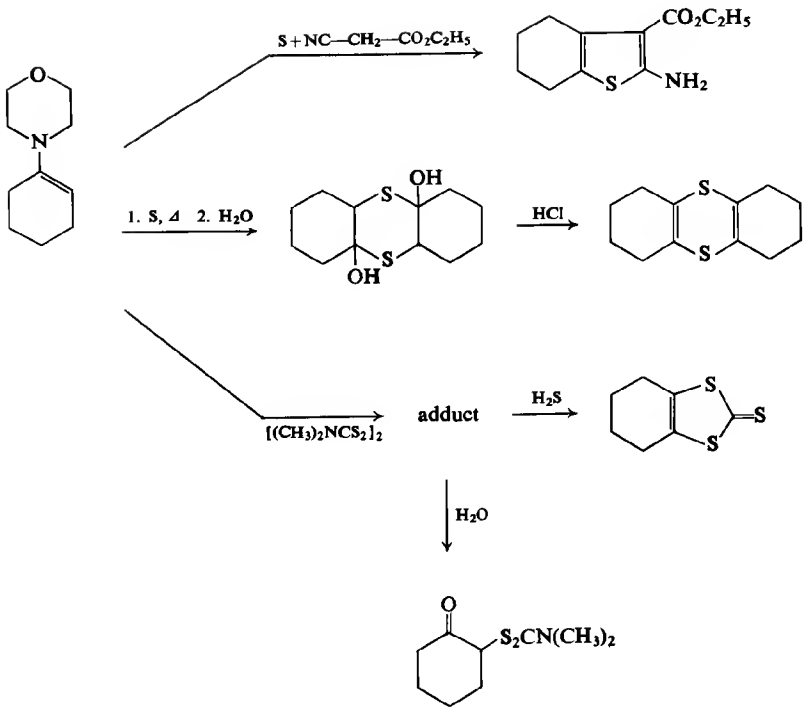


From the reactions of sulfur and carbon disulfide with cyclic ketone-derived enamines (*570–573*) 3H-1,2-dithiole-3-thiones were obtained, whereas the addition of carbon disulfide to other enamines gave α-dithiopyrones (*574*), through initial dimerization of the enamine.

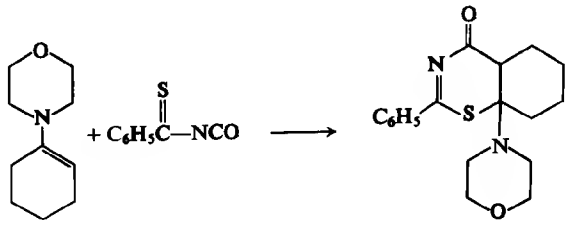


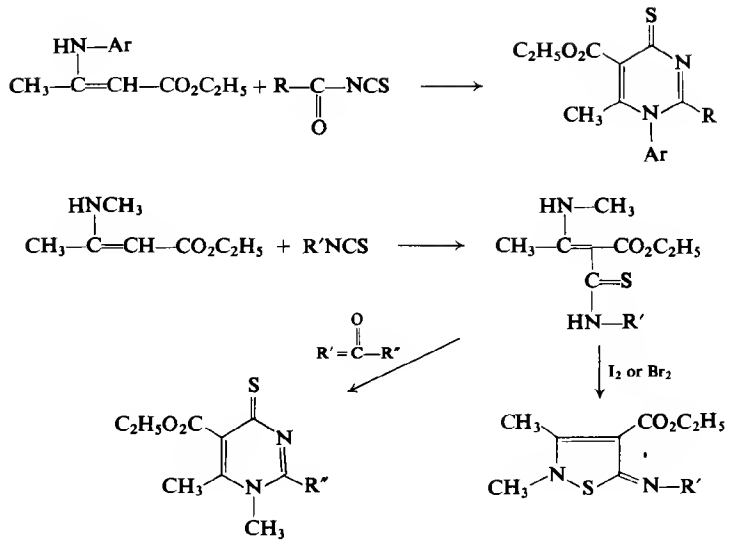


Sulfur has also been added to the condensation product of enamines with cyanoacetic ester (*575*) and directly to enamines (*576*). A 2H-1,3-dithiol-2-thione was obtained from morpholinocyclohexene and tetramethylthiuram disulfide (*577*).

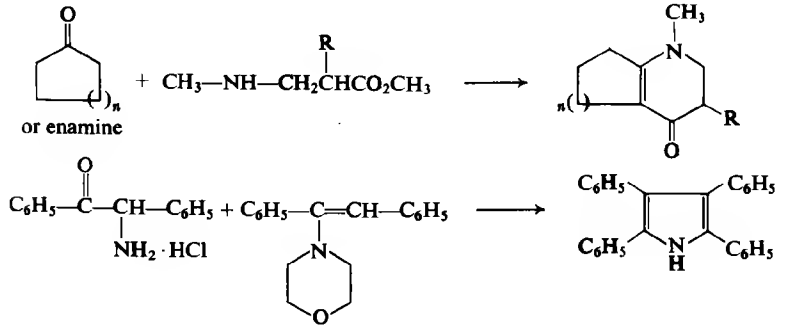


Further variants of the acylation of enamines with subsequent cyclization are found in the use of thioacylisocyanates (*578*) and acylthiocyanates (*579,580*) in heterocyclic syntheses.

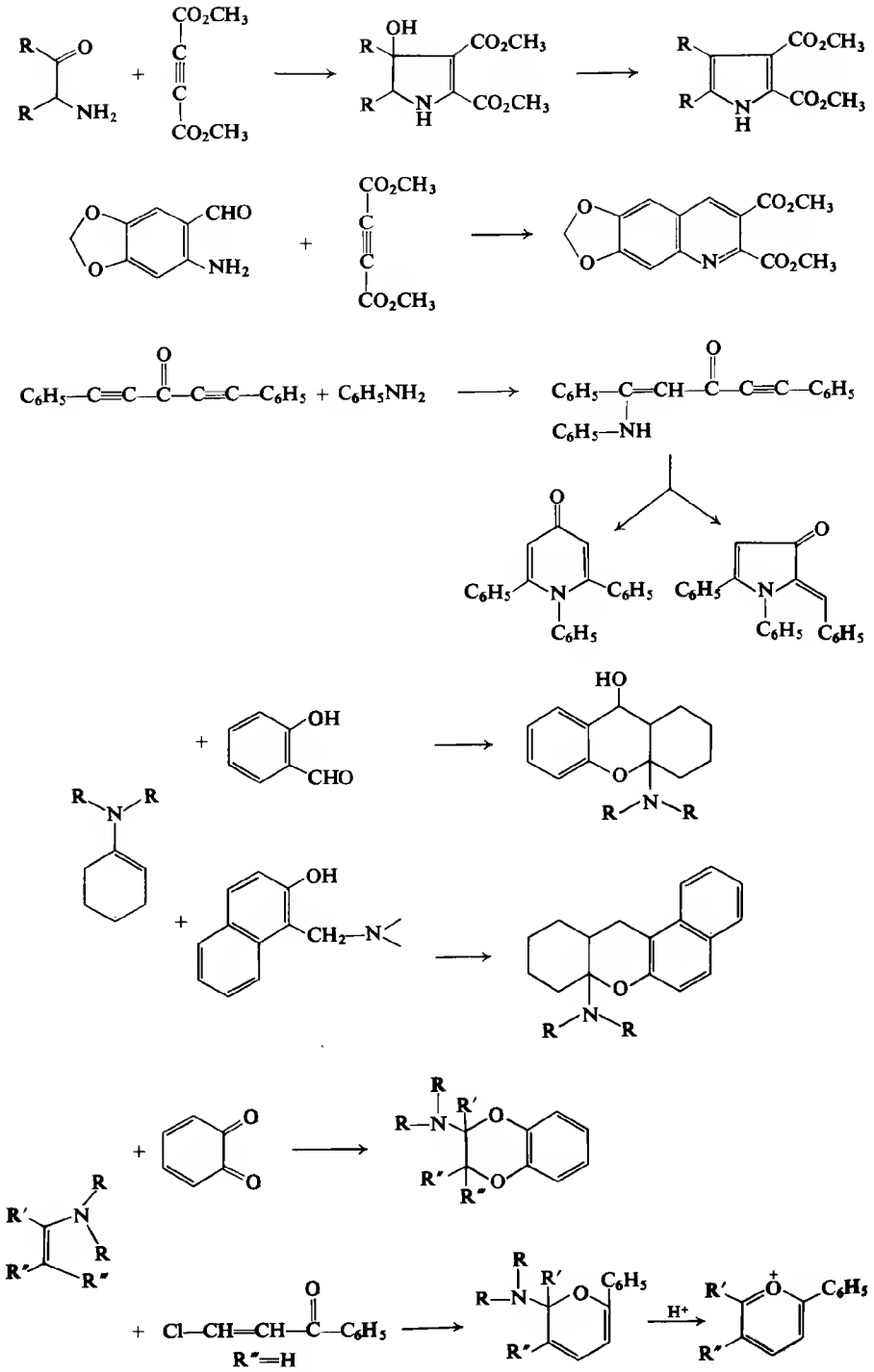




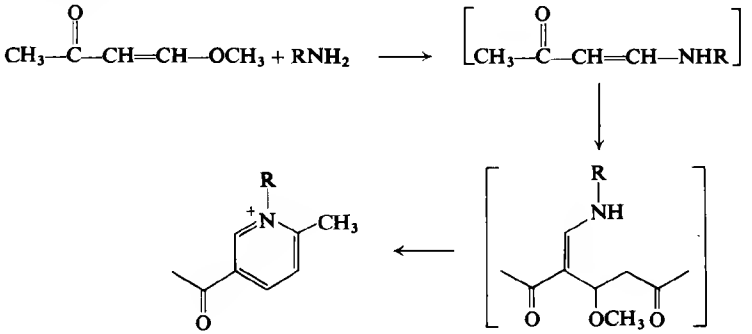
The formation of five- (*362*) and six- (*581*) membered vinylogous lactams and pyrroles by intramolecular enamine acylations has been accomplished in some examples by formation of the cyclization precursor through an initial enamine exchange (*362*).



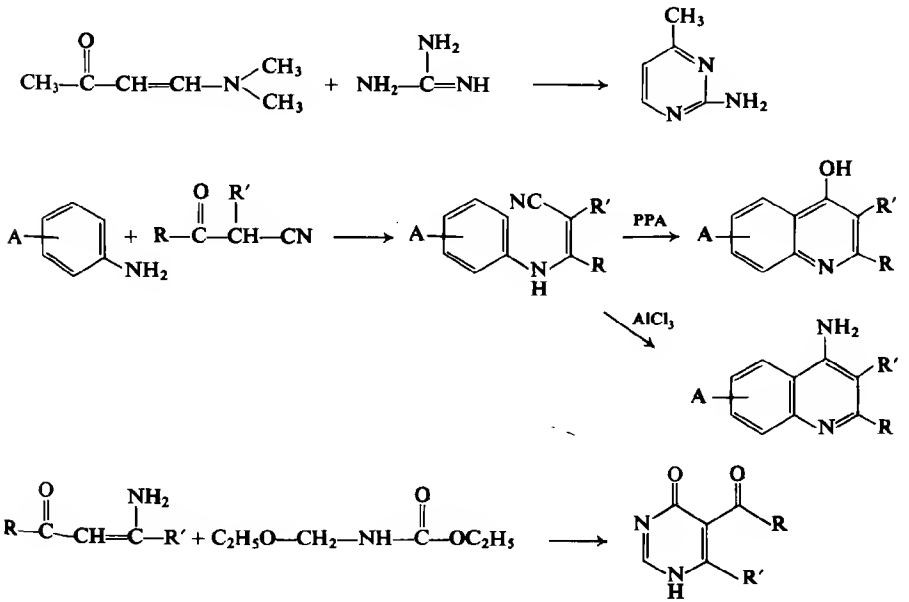
These reactions are related to the formation of pyrroles and quinolines from aminocarbonyl compounds and acetylenes (*582,583*) and may be contrasted with the formation of pyran derivatives by electrophilic attack on an enamine, followed by addition of an oxygen function to the imonium carbon (*584–590*).



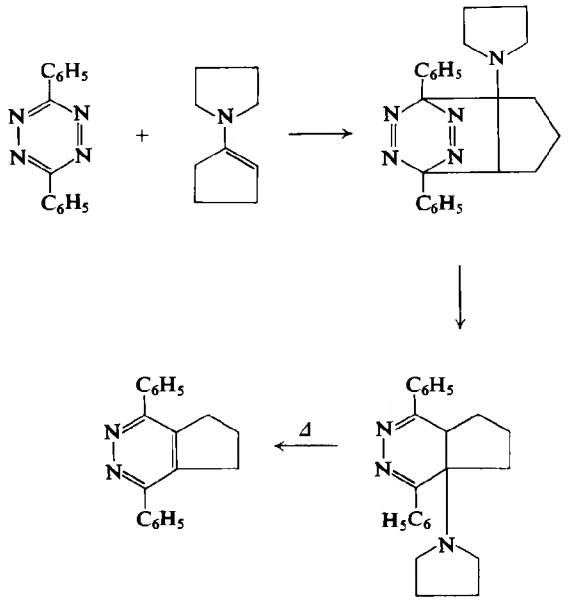
The formation of 3-acylpyridinium compounds (*591*) from primary amines and 1-methoxybutene-3-one can be regarded as the enamine alkylation of a vinylogous amide followed by cyclization and loss of methanol and water.



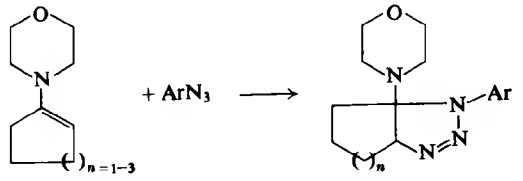
Use of β-dicarbonyl compounds in heterocyclic syntheses is, of course, well established, but an interest in vinylogous amides or vinylogous ureas as reactive intermediates has been increased by the current appreciation of enamine chemistry (*592–594*).

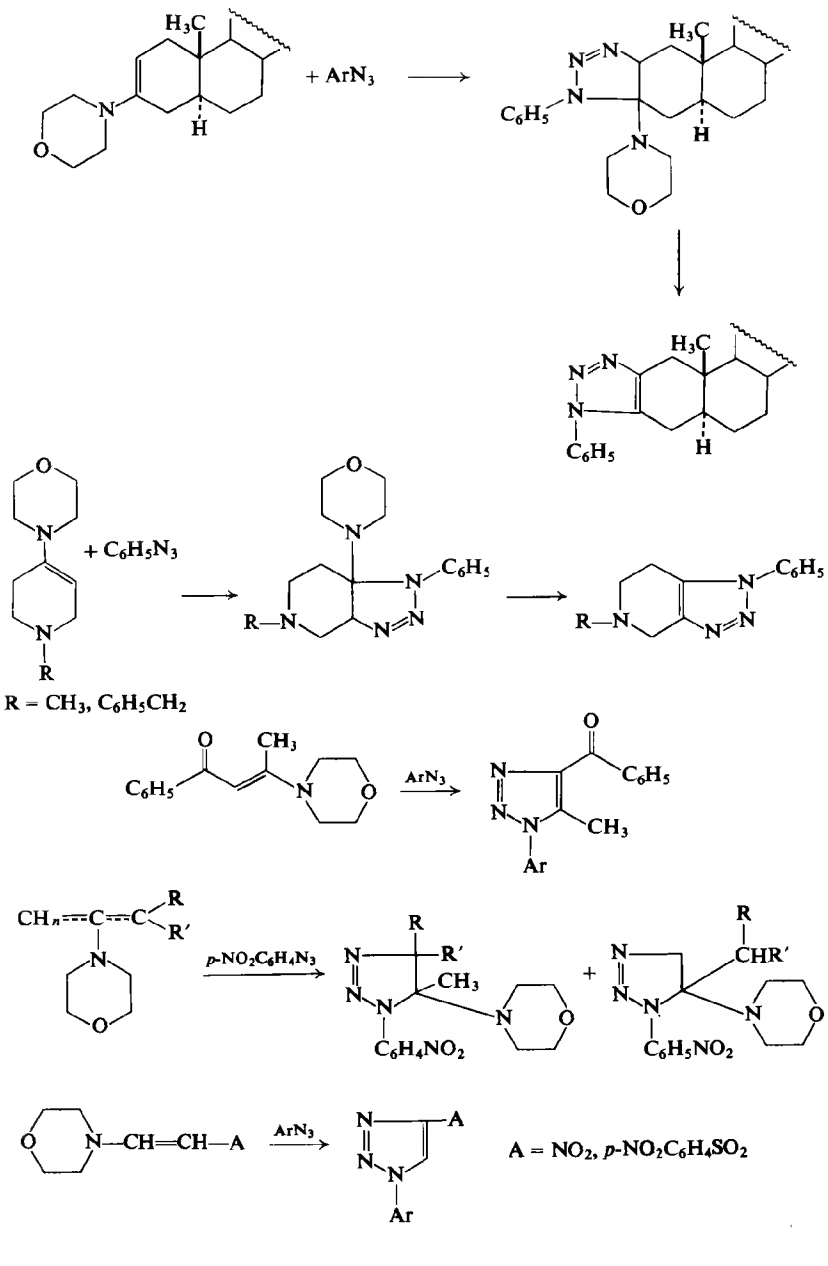


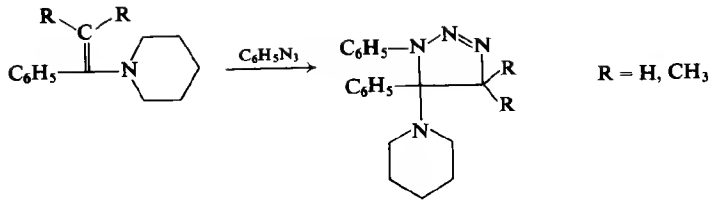
While enamines are poor dienophiles for Diels–Alder reactions, their addition to tetrazines has provided a route to pyridazines (*595*).

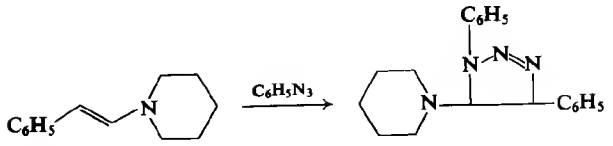


The reactions of enamines as 1,3-dipolarophiles provide the most extensive examples of applications to heterocyclic syntheses. Thus the addition of aryl azides to a large number of cyclic (*596–598*) and acyclic (*599–602*) enamines has led to aminotriazolines which could be converted to triazoles with acid. Particular attention has been given to the direction of azide addition (*601,603*). While the observed products suggest a transition state in which the development of charges gives greater directional control than steric factors, kinetic data and solvent effects (*604–606*) speak against zwitterionic intermediates and support the usual 1,3-dipolar addition mechanism.

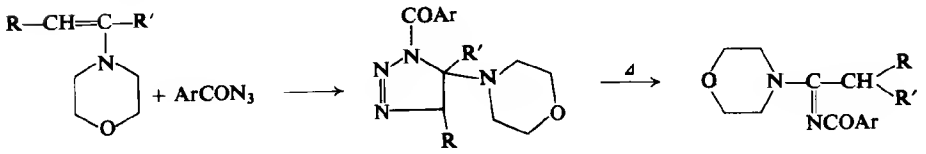


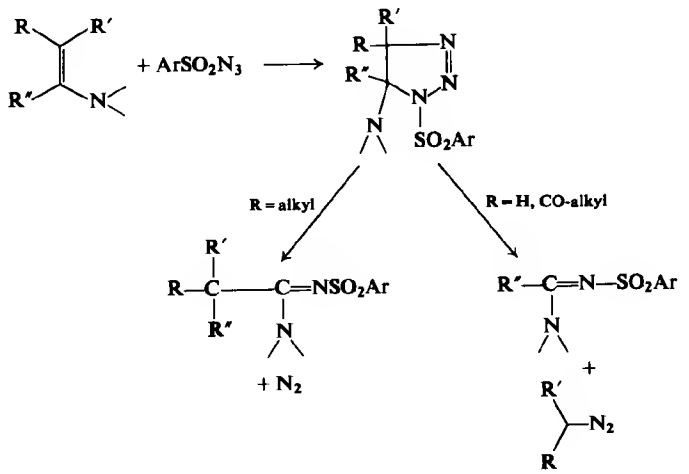




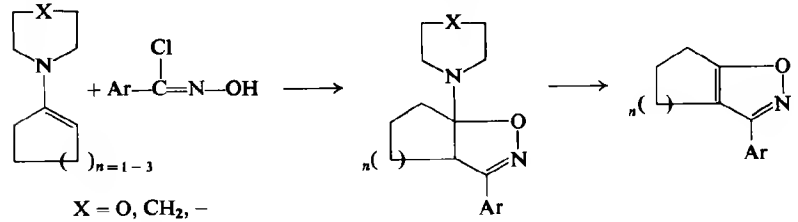


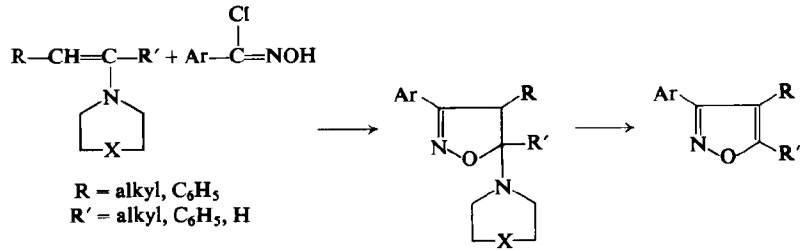
The addition of acylazides leads to less stable triazolines, which lose nitrogen and rearrange to N-acylamidines (*607*). The triazolines obtained from sulfonylazides have been found to follow a similar reaction course as well as a path leading to the generation of diazoalkanes rather than nitrogen (*596,599,608,609*).

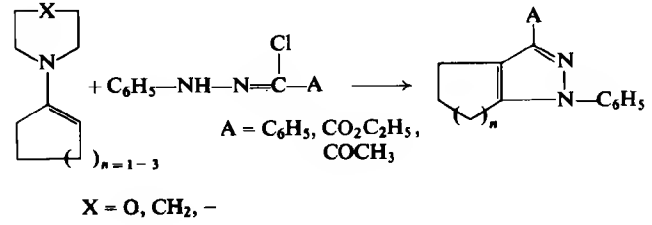


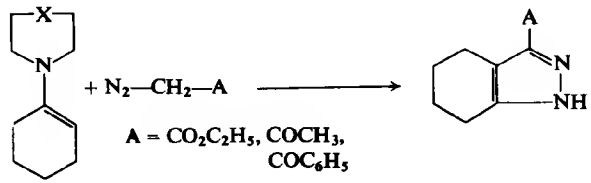


Chloroximes and enamines have provided aminoisoxazolines which could readily be converted to isoxazoles with acid (*610–612*). Pyrrazoles were usually obtained from addition of chlorohydrazones to enamines (*610,613*). The intermediate aminopyrazolines could only be isolated from the reaction of the cyclopentenyl enamine system. Pyrazoles were also obtained from the reactions of enamines with α-diazoketones and α-diazoesters (*614*).

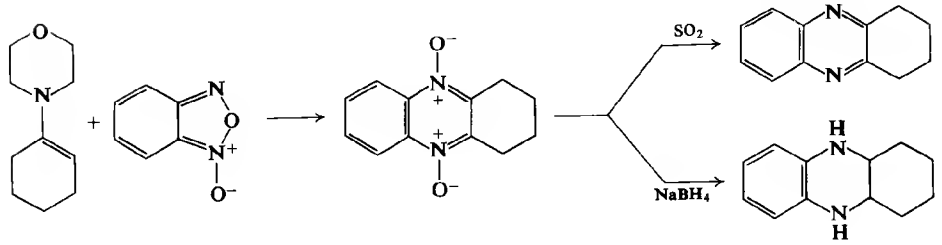


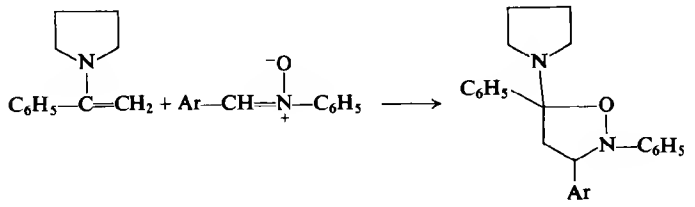


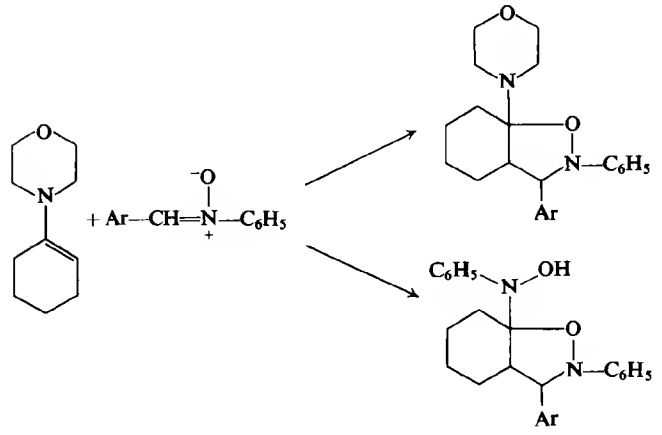




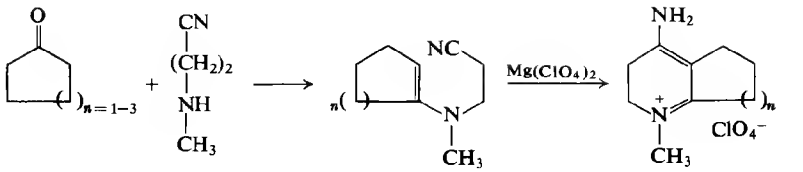
While pyridine N-oxide does not react with enamines in the absence of an acylating agent, other nitrone systems have formed adducts (*615,616*).



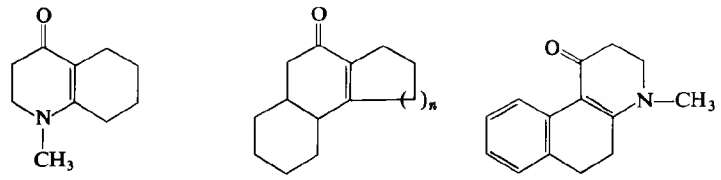


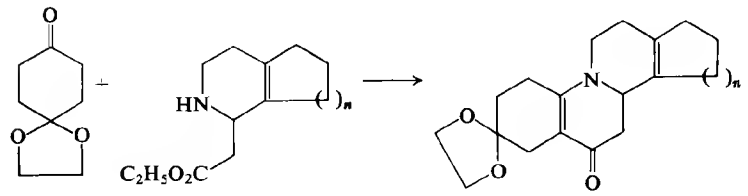


The condensation of ketones with β-aminonitriles or β-aminoesters a cyclization to 4-pyridone derivatives was expanded (*717–719*).

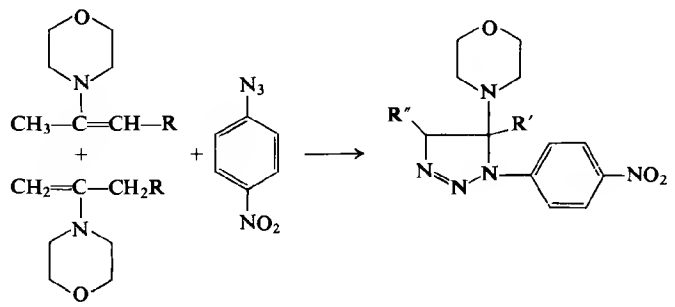


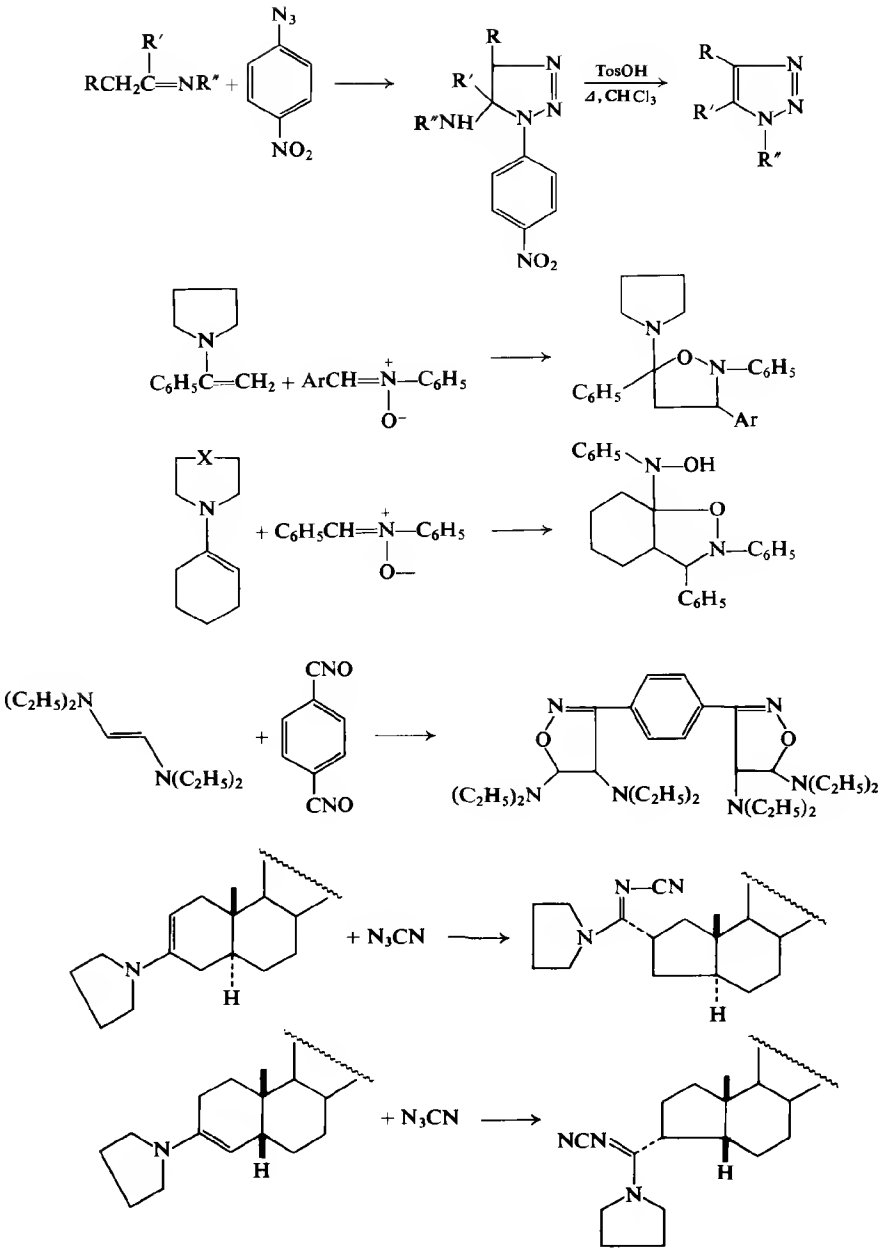
Thus also:





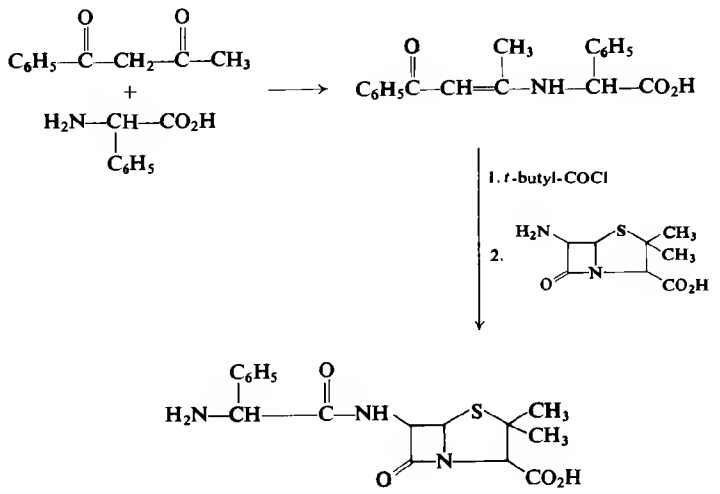
Extensions of 1,3-dipolar additions of aromatic azides (*720,721*) to other enamines (*636*), and particularly to the enamine tautomer of Schiff's bases, were explored (*722,723*). Further nitrone additions were reported (*724,725*) and a double nitrile oxide added to an endiamine (*647*). Cyanogen azide and enamines gave cyanoamidines through rearrangement (*726*).





XVIII. Enamines as Protecting Groups

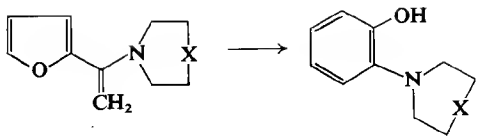
The formation of vinylogous amides from primary amines and β-dicarbonyl compounds gives rise to hydrolyzable amine derivatives with greatly decreased nucleophilicity of the nitrogen function. Thus these derivatives have found some use as protecting groups in peptide syntheses (*617–619*).



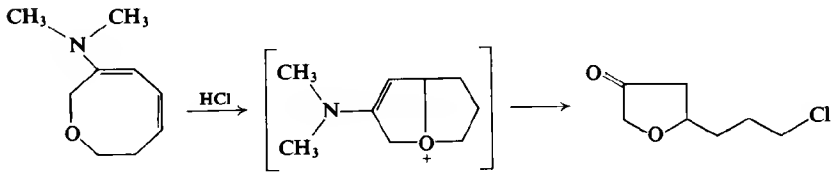
Use of the imonium group for protection of enones was explored. Stability to peracids, lead tetraacetate, bromine, and acetic anhydride was claimed (*727*). The usual resistance of enamines (but not their salts) to additions of Grignard reagents was used for selective addition to a 3,17-diketosteroid by formation of the usual 3-monoenamine (*728*).

XIX. Rearrangements of Enamines and Reactions where Enamines Occur as Intermediates

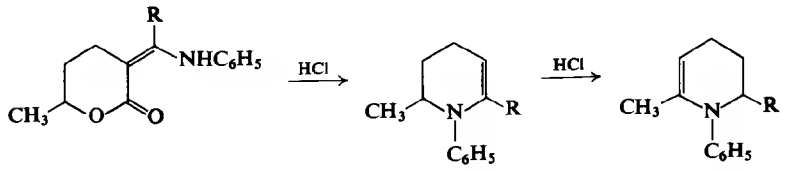
The formation of enamines from carbonyl compounds and secondary amines usually entails as only questionable structural feature, the possible isomeric position of double bonds in the product. Molecular rearrangements have not presented synthetic limitations. A notable exception is the generation of *o*-aminophenols on distillation of enamines derived from 2-acylfurans (*620,621*).



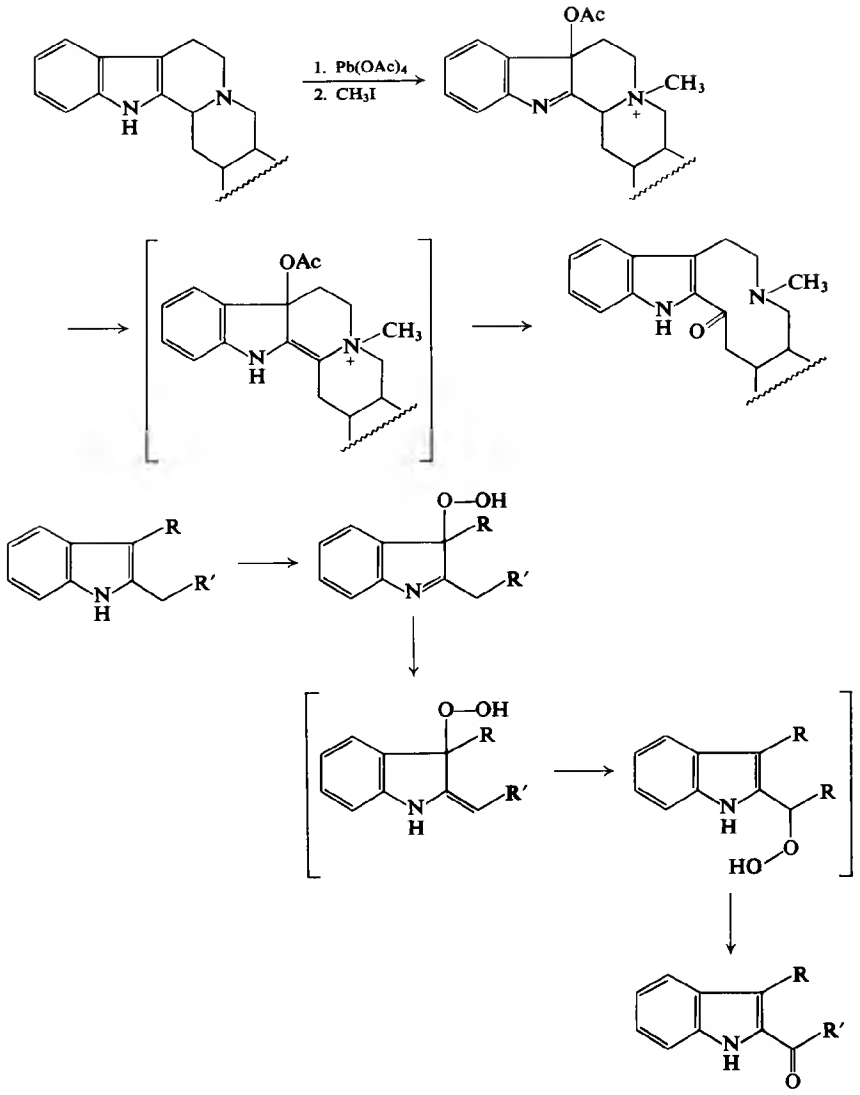
Molecular rearrangements in the reactions of enamines have also not restricted their synthetic applications. Skeletal rearrangements were shown above in the ring expansion or cleavage reactions of initially formed four-membered-ring adducts of enamines and in the decomposition of aryl and sulfonyl azide products. Structural changes may, however, also occur in the reactions of enamines with acids. The reported contraction of an eight-membered-ring oxygen containing dienamine in acid may arise through an oxonium salt formed by transannular delocalization of positive charge on the imonium salt of the dienamine system (*622*).



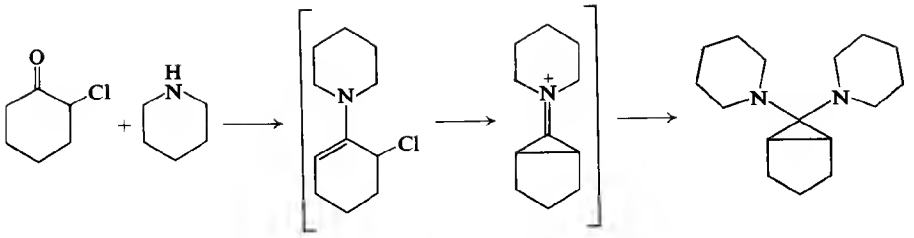
Rearrangements of vinylogous urethanes to vinylogous carbonic acids and decarboxylation are other interesting enamine rearrangements which may be synthetically useful in the formation of cyclic enamines (*623,624*).



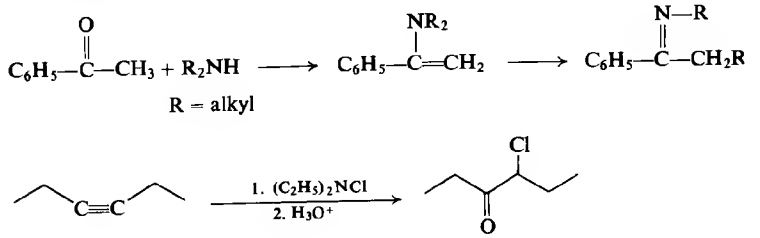
The enamine–imine tautomerism of the indolenine system gives rise to rearrangement reactions of interest in indole alkaloid chemistry. Thus the synthesis of dihydroburnamicine (*625*) utilized the rearrangement of an acetoxyindolenine to an α-hydroxyalkyl indole, presumably through an intermediate enamine. Similarly 2,3-dialkyl indoles undergo oxidations to 2-acyl indoles (*626–631*).



In the reaction of 2-chlorocyclohexanone with a secondary amine (*632*) one encounters an intramolecular enamine alkylation analogous to the internal alkylations which constitute the critical step of some Favorskii rearrangements.



Rearrangement of an enamine to a Schiff's base through N- to C-alkyl migration was reported (*729*). These authors also found that enamines, rather than aminals, were formed from butyraldehyde and secondary amines (*730*). Chloramines and acetylenes reacted to give chloroenamine intermediates, which hydrolyzed on work-up of the reactions (*731*).



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ENAMINES: SYNTHESIS, STRUCTURE, AND REACTIONS

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